2013-1662

United States Court of Appeals for the Federal Circuit

ENDO PHARMACEUTICALS INC.,

Plaintiff-Appellant,

v.

ROXANE LABORATORIES, INC.,

Defendants-Appellee.

Appeal from the United States District Court for the Southern District of New York in Case No. 13-CV-3288, Senior Judge Thomas P. Griesa

NON-CONFIDENTIAL PRINCIPAL BRIEF FOR PLAINTIFF-APPELLANT ENDO PHARMACEUTICALS INC.

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October 2, 2013

CERTIFICATE OF INTEREST

Counsel for the Plaintiff-Appellant, Endo Pharmaceuticals Inc., certifies the following:

1. The full name of every party or amicus represented by me is:
Endo Pharmaceuticals Inc.

2. The name of the real party in interest (if the real party named in the caption is not the real party in interest) represented by me is: N/A.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

Endo Health Solutions Inc. is the parent corporation of Endo Pharmaceuticals Inc. Endo Health Solutions, a publicly traded company, owns more than 10% of Endo Pharmaceuticals Inc. No other publicly traded company owns 10% or more of Endo Pharmaceuticals Inc.'s stock.

4. The names of all law firms and the attorneys that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court are:

In the Southern District of New York, Endo Pharmaceuticals Inc. was represented by Martin J. Black, Robert D. Rhoad, Ann C. Pease, Jonathan D. Loeb, George Gordon, and Joshua Sherman of Dechert LLP. On appeal before this Court, Endo Pharmaceuticals Inc. is represented by Martin J. Black, Robert D. Rhoad, Jonathan D. Loeb, Joseph R. Heffern, and Vincent A. Gallo of Dechert LLP.

Date: October 2, 2013

/s/ Martin J. Black

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CONFIDENTIAL MATERIAL OMITTED

Material has been redacted from pages 6-7, 10, 13-17, 20-21, 25-29 and 33-34 of Principal Brief for Plaintiff-Appellant Endo Pharmaceuticals Inc. This material is deemed confidential business information within the meaning of Rule 26(c)(1)(G) of the Federal Rules of Civil Procedure. The material omitted from these pages contains Appellant's and Appellees' confidential financial and business information.

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I. STATEMENT OF RELATED CASES

This interlocutory appeal is related to *Endo Pharmaceuticals Inc. v. Actavis, Inc., et al.*, No. 13-1658 ("*Actavis* appeal"), which is also currently pending before this Court. Both appeals are part of a series of related, ongoing Hatch-Waxman Act patent litigations that Appellant Endo Pharmaceuticals Inc. ("Endo") has filed against a number of generic drug manufacturers which are pending in the U.S. District Court for the Southern District of New York, and are assigned to U.S. District Court Judge Thomas P. Griesa.

Those cases are: *Endo Pharmaceuticals Inc., et al. v. Teva Pharmaceuticals USA, Inc., et al.*, 12-cv-8060 (TPG); *Endo Pharmaceuticals Inc., et al. v. Amneal Pharmaceuticals LLC, et al.*, 12-cv-8115 (TPG); *Endo Pharmaceuticals Inc., et al. v. Impax Laboratories, Inc., et al.*, 12-cv-8317 (TPG); *Endo Pharmaceuticals Inc., et al. v. Sandoz Inc.*, 12-cv-8318 (TPG); *Endo Pharmaceuticals Inc. v. Actavis Inc., et al.*, 12-cv-8985 (TPG); *Endo Pharmaceuticals Inc., et al. v. Par Pharmaceutical Co., Inc., et al.*, 12-cv-9261 (TPG); *Endo Pharmaceuticals Inc., et al. v. Impax Laboratories, Inc.*, 13-cv-435 (TPG); *Endo Pharmaceuticals Inc., et al. v. Actavis Inc., et al.*, 13-cv-436 (TPG); *Endo Pharmaceuticals Inc. v. Mallinckrodt LLC*, 13-cv-3286 (TPG); *Endo Pharmaceuticals Inc. v. Sandoz Inc.*, 13-cv-3287 (TPG); *Endo Pharmaceuticals Inc. v. Roxane Laboratories, Inc.*, 13-cv-3288 (TPG); *Endo Pharmaceuticals Inc. v. Par Pharmaceutical Companies, Inc. et al.*, 13-cv-3284

(TPG); *Endo Pharmaceuticals Inc. v. Ranbaxy Laboratories Ltd., et al.*, 13-cv-4343 (TPG).

In each of those twelve other suits, as well as in this and the related *Actavis* appeal, the defendants are generic manufacturers that have filed Abbreviated New Drug Applications seeking approval from the Food and Drug Administration ("FDA") to market generic versions of Endo's Opana® ER tablets (either the currently marketed, crush-resistant formulation thereof, or an earlier, now discontinued formulation); and in each instance, Endo asserts claims against the generic manufacturers for infringement of the same three patents that are at issue in this action. In some of those actions, Endo filed suit as co-plaintiff with Grünenthal GmbH on three additional patents that Grünenthal owns and has exclusively licensed to Endo in the relevant field of use.

This appeal and the *Actavis* appeal stem from the same order by the district court, rendered orally from the bench on September 12, 2013 (JA06433-JA06439) (and subsequently confirmed by written order on September 18, 2013 (JA00001-JA00002)), denying Endo's motions for a preliminary injunction against Appellees Roxane Laboratories, Inc. ("Roxane") and Actavis Inc. and Actavis South Atlantic LLC (collectively, "Actavis"), seeking to enjoin them from launching their proposed generic versions of Endo's Opana® ER tablets prior to a trial on the merits of Endo's patent claims.

Endo has filed an unopposed motion to consolidate this appeal and the *Actavis* appeal. That motion is still pending before the Court.

II. JURISDICTIONAL STATEMENT

The district court has subject matter jurisdiction under 28 U.S.C. §§ 1331 and 1338(a). This Court has appellate jurisdiction under 28 U.S.C. § 1292(a)(1), because Endo is appealing from the district court's interlocutory order denying Endo's motion under Federal Rule of Civil Procedure 65(a) for a preliminary injunction. Endo timely filed a Notice of Appeal, which was entered on the docket on September 18, 2013.

III. STATEMENT OF THE ISSUES

1. Whether the district court abused its discretion in denying Endo's motion for a preliminary injunction based upon an alleged implied license and estoppel, without first ascertaining the scope of the express rights granted under the parties' settlement agreement?

2. Whether the district court erred in concluding Endo was estopped from asserting the patents in suit by a prior license where the license and negotiating history demonstrated that Roxane obtained a limited license rather than a license to all of Endo's patents?

IV. STATEMENT OF THE CASE

Endo filed its Complaint on May 15, 2013, alleging that Roxane's non-crush resistant, generic version of Opana® ER infringed the following U.S. Patents

owned by Endo: U.S. Patent Nos. 8,309,122 ("the '122 patent") (JA00046); 8,329,216 ("the '216 patent") (JA00078); and 7,851,482 ("the '482 patent") (JA00017) (collectively, "the patents-in-suit").

Roxane answered the Complaint on July 15, 2013, asserting affirmative defenses and counterclaims that, *inter alia*, the patents-in-suit were licensed and "invalid for failure to comply with one or more of the provisions of Title 35 of the United States Code, including, but not limited to, §§ 101, 102, 103 and/or 112." (JA00517-JA00518).

In July, Roxane received FDA approval to launch its generic tablets. Shortly thereafter, Endo moved for a preliminary injunction, seeking to enjoin Roxane from launching its generic tablets prior to a trial on the merits of Endo's infringement claims. (JA00523).

On August 26, 2013, the district court held an initial conference on that motion, as well as the co-pending preliminary injunction motion that Endo filed at the same time in the related *Actavis* action, and decided to first consider license defenses raised by Roxane and Actavis during the conference, before considering the remaining issues raised by Endo's motions. (JA006388-JA06390). Roxane filed an opposition brief, confined solely to the licensing issue, on September 3, 2013. Endo subsequently filed a unified reply brief responding to both Roxane's and Actavis's opposition briefs on September 10, 2013, which as requested by the

district court, was limited to Roxane's and Actavis's license defenses. (JA06387-JA06390).

On September 12, 2013, the district court conducted the hearing to address Roxane's and Actavis's license defenses. The district court denied Endo's motion from the bench, and indicating that it would not be issuing a written decision explaining its reasoning. (JA06433-JA06439).

Endo immediately moved orally for an injunction enjoining Roxane and Actavis from launching their generic tablets pending an expedited appeal to this Court, but the district court denied that motion. (JA06439-JA06447).[1]

Endo filed a notice of appeal seeking reversal of the district court's denial of a preliminary injunction. (JA05233). Endo thereafter filed an unopposed motion to expedite the briefing and oral argument schedule for this appeal, which this Court granted on September 25, 2013.

[1] Roxane, has agreed to give Endo 30-days advance notice of any intent to launch, and as yet, has not given that notice to Endo. (JA06378). Accordingly, although Roxane has refused to agree not to launch until the appeal in its case is resolved, in view of its promise to give Endo 30-days advance notice, Endo has not moved for an injunction pending appeal in this case, but will so move if Roxane notifies Endo that it intends to launch prior to resolution of this appeal.

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V. STATEMENT OF THE FACTS

A. OVERVIEW OF THE TECHNOLOGY

1. ENDO'S OPANA® ER TABLETS

Endo is a specialty pharmaceutical company engaged in the research, development, sale, and marketing of prescription pharmaceutical products used, among other things, to treat and manage pain. (JA00775). Endo's premier branded product is OPANA® ER, an extended-release ("ER") pain medication that contains oxymorphone hydrochloride, a morphine-like opioid narcotic, as the sole active ingredient. (JA00775, JA01300-JA01301). OPANA® ER generates hundreds of millions of dollars in annual net sales revenue [redacted]

OPANA® ER tablets employ a controlled release formulation that slowly delivers oxymorphone into the bloodstream in order to achieve a sustained therapeutic effect, and are approved for a 12-hour, or twice a day, dosing interval. (JA01300-JA01301). [redacted] Like other extended release opioid pain medications (such as, for

example, OxyContin®), OPANA® ER tablets proved to be subject to potential abuse, most commonly by drug abusers who crush and then snort the tablets. (JA00779)

In an effort to stem that abuse, Endo [redacted] a reformulated, crush resistant formulation ("CRF") of OPANA® ER.[2] (JA00777, JA00779). FDA approved the new, crush-resistant version of OPANA® ER ("OPANA® ER CRF") in December 2011. (JA00779). Endo thereafter discontinued the original, non-crush-resistant version of OPANA® ER ("OPANA® ER Original Formulation"), and now sells only the new, crush-resistant tablets. (JA00779-JA00780).

2. THE PATENTS-IN-SUIT

Two of the three patents in suit—the '122 and '216 patents—are related patents that share a common specification. (JA00046, JA00078). Broadly speaking, both patents are directed to controlled-release oxymorphone formulations that result in particular therapeutically effective levels of oxymorphone in a patient's bloodstream, and release the oxymorphone at a

[2] *See, e.g.,* FDA draft *Guidance for Industry: Abuse-Deterrent Opioids--Evaluation and Labeling*, in which FDA stated that the "[a]buse and misuse of [prescription opioid pain medications] have created a serious and growing public health problem," and that it considers the development of abuse-deterrent formulations to be a "high public health priority." (JA00650).

desirable rate as shown via *in vitro* dissolution tests and/or *in vivo* pharmacokinetic tests. (JA00650).

For example, representative Claim 1 of the '122 patent recites:

> 1. An analgesically effective controlled release pharmaceutical composition with a twelve hour dosing interval in the form of a tablet, comprising
>
> oxymorphone or a pharmaceutically acceptable salt thereof as the sole active ingredient in the tablet, and
>
> a controlled release delivery system comprising at least one pharmaceutical excipient,
>
> wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37 °C.,
>
> about 15% to about 50% by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.

(JA00045).

Representative Claim 1 of the'216 patent recites:

> 1. An oral controlled release oxymorphone formulation, comprising:
>
> about 5 mg to about 80 mg of oxymorphone or a pharmaceutically acceptable salt of oxymorphone; and
>
> a hydrophilic material,
>
> wherein upon oral administration of the formulation to a subject in need of an analgesic effect:
>
> (i) the formulation provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone;
>
> (ii) the blood plasma levels of 6-OH oxymorphone and oxymorphone peak within about 1 hour to about 8 hours after administration;

(iii) the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of area under the curve ($AUC_{(0\ to\ inf)}$) of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5;

(iv) the duration of the analgesic effect is through at least about 12 hours after administration; and

(v) the blood plasma levels of oxymorphone exhibit two or three peaks within about 12 hours after administration.

(JA00074).

The '122 and '216 were each filed as continuations of U.S. patent application No. 10/190,192 (the "parent '192 application"). (JA04868-JA04869, JA00046, JA00078). In addition, both of these patents claim priority to four earlier filed provisional applications. (JA04868-JA04869, JA00046, JA00078). These facts are evident from both the face page of the patents, as well as the first column of their specifications—*see, e.g.* the following excerpts from the '122 patent:

Related U.S. Application Data

(63) Continuation of application No. 10/190,192, filed on Jul. 3, 2002.

(60) Provisional application No. 60/303,357, filed on Jul. 6, 2001, provisional application No. 60/329,432, filed on Oct. 15, 2001, provisional application No. 60/329,444, filed on Oct. 15, 2001, provisional application No. 60/329,445, filed on Oct. 15, 2001.

(JA04868-JA04869, JA00018).

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RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 10/190,192 filed Jul. 3, 2002 and claims priority to U.S. Provisional Patent Application Ser. Nos. 60/329,445 filed Oct. 15, 2001, 60/329,432 filed Oct. 15, 2001, 60/303,357 filed Jul. 6, 2001, and 60/329,444 filed Oct. 15, 2001, [1] which are incorporated herein by reference to the extent permitted by law.

(JA04868-JA04869, JA00033) (emphasis added). The exact same language appears on the face page and in the first column of the '216 patent. (JA00062).

The third patent-in-suit—the '482 patent—is directed to, among other things, a method for purifying oxymorphone hydrochloride and the resultant highly purified oxymorphone hydrochloride. Endo acquired the '482 patent from Johnson Matthey in March 2012. (JA04869). [redacted]

3. ROXANE'S GENERIC TABLETS

Companies seeking to market a new pharmaceutical drug must first obtain approval from the FDA, typically through the filing of a New Drug Application

[3] [redacted]

("NDA"). *See* 21 U.S.C. § 355(a). The so-called "Hatch-Waxman Act,"[4] however, authorizes a generic manufacturer seeking to market a generic version of an existing brand name drug to file an Abbreviated New Drug Application ("ANDA"), rather than a full-blown NDA, that piggybacks upon the safety and efficacy data that the innovator company included in its NDA. *See* 21 U.S.C. § 355(j). Under that Act, the filing of an ANDA seeking approval to market a generic product prior to the expiration of a patent covering the brand name product is an act of patent infringement. *See* 35 U.S.C. § 271(e)(2). The Act further provides that, under certain circumstances, the first ANDA filer may be entitled to 180 days of marketing exclusivity, during which time no other ANDA filer may come to market with a competing generic product. *See* 21 U.S.C. § 355(j)(5)(B)(iv).[5]

Here, generic manufacturers have filed fifteen separate ANDA applications seeking approval to market generic versions of OPANA® ER. Seven of those ANDAs relate to the original, non-crush resistant formulation of OPANA® ER, including the Roxane ANDA (No. 20-0822) that is at issue in this case.

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[4] Pub. L. No. 98-417, *codified at* 21 U.S.C. §§ 355, 360cc, and 35 U.S.C. §§ 156, 271, 282.

[5] For a more detailed description of the Hatch-Waxman Act framework and ANDA patent infringement litigation arising thereunder, *see Caraco Pharmaceutical Laboratories, Ltd. v. Forest Laboratories, Inc.*, 527 F.3d 1278, 1282-86 (Fed. Cir. 2008).

B. PRIOR LITIGATION AND SETTLEMENT

In 2009, Roxane filed its ANDA seeking FDA approval to make generic versions of Endo's original Opana® ER tablets. In response, Endo sued Actavis for infringement of only one patent: U.S. Patent No. 5,958,456 ("the '456 patent"). (JA04858-JA04859).[6] The '456 patent expired in September 2013 (*id.* at ¶ 6) and is not related to any of the patents now in suit.

At the time, there were three other patents listed in FDA's "Orange Book" with respect to Opana® ER: U.S. Patent No. 5,128,143 ("the '143 patent"); U.S. Patent No. 5,662,933 ("the '933 patent"); and U.S. Patent No. 7,276,250 ("the '250 patent"). (JA04859). Roxane served a so-called "Paragraph IV notice" asserting that its generic tablets would not infringe those patents. Endo agreed, and therefore never sued Roxane over them. (*Id.* at ¶ 8). The '250 patent, for example, is directed to pharmaceutical formulations that include locust bean gum, xanthan gum, dextrose, calcium sulfate dehydrate, and ethyl cellulose, none of which are in Roxane's generic tablets. (JA04884).

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[6] Endo was the exclusive licensee of the '456 patent, but Penwest Pharmaceuticals Co. ("Penwest") had title to it. Thus, Endo and Penwest were co-plaintiffs in the litigation, and both were parties to the settlements with Roxane. Endo has since acquired Penwest (JA04859), and for ease of reference, in describing the prior litigation and settlement, Endo will refer to itself and Penwest collectively as "Endo."

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Endo and Roxane settled the litigation by agreement dated as of May 4, 2011, [redacted]

The negotiating history was as follows. In August 2010, Endo sent a draft term sheet proposing to [redacted]

Roxane responded with a proposal that would have dramatically expanded the scope of the licensed patents to include [redacted]

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[redacted] Endo replied by adding a clause that narrowed the licensed patents to [redacted]

Roxane then sent another revision in which it again sought to broaden the scope of the patents to be licensed. (JA04958-JA04959 at § 6). In particular, Roxane created a defined term, the "Licensed Patents," which it defined as follows:

[redacted]

(*Id.* (emphasis added, original underlining removed)). In other words, Roxane sought to obtain a license [redacted]

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Endo rejected Roxane's proposal, and responded with a counter-proposal narrowing the scope of patent applications to include only [redacted]

[redacted]

(JA04966-JA04967 at § 6) (the draft was "redlined" to show insertions as underlined text, and deletions as struck through text) (bold/italics added).

Roxane accepted Endo's counter-proposal, and the parties thereafter negotiated the terms of a full-blown Settlement and License Agreement over the course of five months. (JA04865at ¶ 30). Although the language used in defining the term "Licensed Patents" was tweaked for clarity, the scope of the patents and patent applications within that definition remained substantially the same as was previously agreed upon. In particular, the agreement as executed (the "Agreement") defines "Licensed Patents" as follows:

[redacted]

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[redacted]

(JA04865-JA04866, JA04973 at § 1.16 (emphasis added)). Thus, as agreed upon by the parties, the "Licensed Patents" [redacted]

Moreover, Endo and Roxane agreed that the license obtained by Roxane would be [redacted]

Furthermore, during the course of the negotiation of the Agreement, Roxane sought to include a provision pursuant to which Endo [redacted] That provision would have precluded Endo from, among other things, [redacted]

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[redacted]

[redacted]

C. The DISTRICT COURT'S RULING

In the present action, Endo asserts claims for infringement of the '122, '216, and '482 patents, all of which issued *after* the settlement and therefore were *not* at issue in the prior litigation.[7]

Endo moved for a preliminary injunction, seeking to enjoin Roxane from launching its ANDA tablets prior to a trial on the merits of Endo's infringement claims. (JA00535). In response, Roxane did not dispute that its tablets infringe the patents-in-suit, but contended that pursuant to the parties' Agreement, it has a license under the '122 and '216 patents because those patents claim a "common priority" with the '250 patent to the same provisional application, and therefore purportedly are within the defined scope of the "Licensed Patents." (JA04817).

On September 12, 2013, the district court conducted a hearing to address Roxane's license defenses (as well as the license defenses that Actavis asserted in the related *Actavis* case). The district judge candidly admitted that he was sitting "almost as a layman." He thought that suing on later-issued patents "sounds terribly unfair," and went on to state: "I mean, that just sounds like – is this

[7] The PTO issued the '216 and '122 patents only after this Court reversed the PTO's finding that they were unpatentable over the prior art. *See In re Huai-Hung Kao*, 639 F.3d 1057 (Fed. Cir. 2011).

America or not? It sounds terrible." (JA06411). The Court had not reviewed the declarations filed by Endo on the negotiating history, and when Endo explained the unrebutted evidence that Roxane had explicit negotiations over this issue during which Endo told Roxane that it was not going to get a license to the then-pending '122 and '216 patent applications, the court dismissed that crucial information as "not saying anything which is very helpful to me." (JA06411-JA06412). The court had great difficulty in understanding the relationship between the licensed '250 patent and the new patents now in suit. (*See, e.g.,* JA06414, JA06417-JA06418).[8]

At the end of the hearing, the district judge denied the motion stating that he would not write an opinion because the record was full of the essential facts and they did not need to be repeated. (JA06433-JA06434). He then went on to erroneously state that the settlement led to a substantial effort on the part of Actavis and Roxane in response to the settlements (JA06434-JA06435), for which there was no record evidence. After a colloquy on the '482 patent, the court stated that "I'm not claiming to be greatly informed about '482." (JA06436). He then

[8] (JA06414) ("Well, I have to confess to you, I don't understand what you're saying. I'm trying to. . . . I don't quite understand it."); (JA06417-JA06418) ("I'm not taking [it] in, as I would like to, what is being presented here. Is there any way you can simplify it or . . . or summarize it? I will be very frank with you; I'm just not taking it in").

summarized his analysis of the scope of the prior license agreements and ruled as follows:

> I wish to say for the record that I do not feel, for purposes of a preliminary injunction motion, that I am able to make any findings on the issues I have just described, and I want to make it clear that that's exactly where I stand. I'm not saying that the plaintiff has not sustained its burden of proof, and I'm not saying that the defense has not sustained whatever burden they need to sustain. I am simply not able to make any findings on the issues which I have just described. Probably my description is not artful, but I think the lawyers here know exactly what I'm talking about. In my view a much more substantial hearing and indeed, a full trial would be necessary to fully explore what is involved in the issues I am talking about now.

(JA06438).

Nevertheless, he found on the basis of the "doctrine of estoppel," unspecified case law, and his view of what is fair, that having settled the prior litigation, Endo is now barred as a matter of law from asserting the patents-in-suit against Roxane. (JA06439). The district court denied Endo's motion without considering any of the other factors relevant thereto (such as, *e.g.,* irreparable harm, balance of the hardships, or the public interest). *Id.* For the same reason, the district court also denied Endo's companion motion in the related *Actavis* case. *See id.*

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VI. SUMMARY OF THE ARGUMENT

The district court's ruling was remarkable because despite admitting that he felt unable to make any findings about what patents the parties intended to be licensed under the terms of their prior settlement, the district judge found Endo was estopped from asserting the patents-in-suit, all of which issued after the settlement. The district court's denial of a preliminary injunction is fraught with error.

The district court erred as matter of law by finding an implied license despite its inability to decipher the patent rights expressly granted under the parties' agreement. Moreover, its finding of an implied license is contradicted by the evidence in the record, including the undisputed evidence that during the parties' negotiations, Roxane sought [redacted]

Roxane should not now be allowed to capture via an implied contract [redacted] That is particularly so because the parties' agreement also included [redacted]

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[redacted]

Indeed, under the circumstances, Endo would have been far better off if it had gone to trial and lost the underlying litigation, rather than settling and being deemed by judicial fiat to have granted an implied license to later-issued patents that it had expressly refused to license during the parties' negotiations. The value of those judicially-imposed implied rights far exceed the value of the rights Roxane actually negotiated for itself.

Accordingly, the Court should reverse the district court's denial of Endo's motion for a preliminary injunction, and remand the matter for proper consideration of the remaining issues raised by that motion.

VII. ARGUMENT

A. STANDARD OF REVIEW

This Court reviews decisions to grant or deny a preliminary injunction for an abuse of discretion. *Procter & Gamble Co. v. Kraft Foods Global, Inc.*, 549 F.3d 842, 847 (Fed. Cir. 2008). A district court abuses its discretion "when its decision is based on clearly erroneous findings of fact, is based on erroneous interpretations of the law, or is clearly unreasonable, arbitrary or fanciful." *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1460 (Fed. Cir. 1998) (*en banc*). *See also Sanofi-*

Synthelabo v. Apotex, Inc., 470 F.3d 1368, 1374 (Fed. Cir. 2006). Here, the district court's ruling was replete with errors of law and clear errors of fact, was unreasonable and arbitrary, and should be reversed.

B. THE DISTRICT COURT ABUSED ITS DISCRETION IN DENYING ENDO'S MOTION FOR A PRELIMINARY INJUNCTION

1. THE DISTRICT COURT ERRED AS A MATTER OF LAW BY HOLDING THAT ESTOPPEL APPLIED WITHOUT MAKING FINDINGS ON THE SCOPE OF THE AGREEMENT

The district court erred as a matter of law by finding that Endo is estopped from asserting the patents-in-suit against Roxane. It is axiomatic that the first step in determining whether there is an implied license arising out of a prior express license is to examine the express license at issue and determine its scope. The district court not only failed to carry out that task, it confessed that it was unable to do so. (JA06414, JA06417-JA06418, JA06437-JA06438).

The district court was obligated to ascertain the scope of rights granted under the parties' Agreement, and evaluate the parties' negotiating history and surrounding circumstances. It failed to do so, implying that entering into a patent license and then suing on later-issued patents was somehow un-American. (JA06411). Under the district court's over-simplistic view of estoppel and fairness, a patentee who settles infringement litigation would always be forever barred from subsequently asserting a patent claim directed to the same product at issue in the earlier litigation—no matter what the parties said in their agreement

and no matter the surrounding circumstances or expectations of the parties. That is not the law.

To the contrary, as this Court has repeatedly recognized, "patent license agreements can be written to convey different scopes of promises not to sue*, e.g.,* a promise not to sue under a specific patent or, more broadly, a promise not to sue under any patent the licensor now has or may acquire in the future." *Spindelfabrik Suessen-Schurr, Stahlecker & Grill BmbH v. Schert & Salzer Maschinenfabrik Aktiengesellschaft*, 829 F.2d 1075, 1081 (Fed. Cir. 1987). *See also General Protecht Group, Inc. v. Leviton Mfg. Co.*, 651 F.3d 1355, 1361-62 (Fed. Cir. 2011). Given that freedom of contract, this Court has made clear that although different categories of conduct can lead to recognition of an implied license, including under theories of equitable or legal estoppel, such "judicially implied licenses are rare under any doctrine." *Wang Laboratories, Inc. v. Mitsubishi Elec. America, Inc.*, 103 F.3d 1571, 1580-82 (Fed. Cir. 1997). In particular, legal estoppel refers to a "narrow category of conduct" in which a patentee "has licensed or assigned a right, received consideration, and then sought to derogate from the right granted." *TransCore, LP v. Elec. Transaction Consultants Corp.*, 563 F.3d 1271, 1279 (Fed. Cir. 2009).

In order to determine whether to imply a license on the grounds that a patentee has granted a right and then sought to derogate from that right, one must

first ascertain the scope of the patent rights granted in the first instance. *See, e.g., AMP Inc. v. U.S.*, 389 F.2d 448, 453 (Ct.Cl. 1968) (to find legal estoppel, it is "necessary to define the property right granted to defendant by plaintiff, and also to show how plaintiff is attempting to derogate or detract from that right"); *TransCore*, 563 F.3d at 1279-80 ("Mark IV's rights under its implied license to the [continuation patent] are necessarily coextensive with the rights it received in the TransCore–Mark IV license agreement"). Yet, that is exactly what the district court by its own admission not only failed to do, but believed it was unable to do. (JA06437-JA06438).

Because the district court failed to make any findings as to the scope of the express license between the parties or the parties' intent, it was in no position to determine what license might or might not have been implied by the prior agreement. The district court erred by summarily curtailing the preliminary injunctive process and declaring the existence of an estoppel.

2. THE EVIDENCE OF RECORD DOES NOT SUPPORT THE FINDING OF AN ESTOPPEL-BASED IMPLIED LICENSE

a. THE IMPLIED LICENSE IS CONTRARY TO THE EXPRESS TERMS OF THE PARTIES' AGREEMENT

It is black-letter law that courts should not imply a contractual obligation that is inconsistent with express provisions in the contract. *Hartford Fire Ins. Co. v. Federated Dept. Stores, Inc.*, 723 F.Supp. 976, 993 (S.D.N.Y. 1989)

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("obligations inconsistent with the terms of a contract cannot be implied"); *Hovensa, L.L.C v. Technip Italy*, 2009 WL 690993, *7 (S.D.N.Y. May 16, 2009).[9]

Before the district court, Roxane argued that it had an express license to the '122 and '216 patents by urging an overly broad and insupportable construction of the Agreement. In particular, Roxane argued that those patents fall within the scope of subsection (b) of "Licensed Patents":

[redacted]

(JA04973 at § 1.16 (emphasis added)).

Roxane's argument is inconsistent with [redacted]

[redacted]

RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 10/190,192 filed Jul. 3, 2002 and claims priority to U.S. Provisional Patent Application Ser. Nos. 60/329,445 filed Oct. 15, 2001, 60/329,432 filed Oct. 15, 2001, 60/303,357 filed Jul. 6, 2001, and 60/329,444 filed Oct. 15, 2001, which are incorporated herein by reference to the extent permitted by law.

[redacted]

9 [redacted]

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(JA00033 and JA00062, at col. 1, lines 6-12 (emphasis added)). As that excerpt makes clear, the '122 and '216 patent are continuations of the '192 application, and also claim priority to the four provisional applications listed therein. [redacted] Accordingly, the '122 and '216 patents [redacted] and therefore, they are not "Licensed Patents" § 1.16(b) of the Agreement.

The parties' Agreement also included [redacted] The implied license found by the district court directly contradicts this express provision in the Agreement.

b. ROXANE'S IMPLIED LICENSE DEFENSE IS ALSO CONTRARY TO THE PARTIES' NEGOTIATING HISTORY

Roxane's implied license defense is also contrary to the parties' negotiating history. Roxane specifically sought a license to [redacted] (JA04863 at ¶25, JA04945 at §6). After Endo rejected that proposal, Roxane sought a license under, among other things, [redacted] (JA04958-JA04959 at § 6). Endo rejected that proposal as well, and

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countered with a revision that limited the definition to [redacted] In sending that revision to Roxane, Endo's counsel noted that he had "made three amendments, two minor, and one to the definition of 'Licensed Patents.'" (JA04963). Thus, he made clear that Endo's revision to the definition of "Licensed Patents" was not a "minor" one. The Agreement adopts Endo's [redacted] (JA04973 at § 1.16(b)).

Recognizing that interpreting the parties' Agreement as written would eviscerate its license defense, Roxane argued that "Licensed Patents" should be interpreted to encompass [redacted] That is not what the Agreement says, and the Court should reject that interpretation as inconsistent with the parties' negotiating history.[10]

Even more tellingly, during the course of the negotiations with Roxane, the parties discussed [redacted]

[10] Endo contends that Roxane's proffered interpretation is inconsistent with the express language of the Agreement, but to the extent any ambiguity exists, the Court may consider parol evidence for the purpose of aiding in the interpretation of the contract. *Eastman Kodak Co. v. Altek Corp.*, 2013 WL 1285293, *12 (S.D.N.Y. Mar. 29, 2013).

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and Endo repeatedly told Roxane it was unwilling [redacted]

[redacted] Thus, it was clear to the parties at the time that the term "Licensed Patents" did not include the '122 and '216 patent applications, and that Endo had reserved the right to sue Roxane if the PTO were to grant patents thereon.

Roxane should not now be allowed to capture via an implied contract the very thing it sought but failed to have included in the Agreement. *See, e.g., Vacuum Concrete Corp. of Am. v. Am. Mach. & Foundry Co.*, 321 F. Supp. 771, 773 (S.D.N.Y. 1971) ("where the parties have considered the matter and deliberately omitted any such obligation, . . . it will not be implied."); *Enzo Biochem, Inc. v. Johnson & Johnson*, 1992 WL 309613, *6 (S.D.N.Y. Oct. 15, 1992) ("In deciding whether to imply a contract term, courts consider the fact that the parties to a contract may have negotiated over and rejected that particular contract term."); *Eastern Electric, Inc. v. Seeburg Corp.*, 427 F.2d 23, 26–27 (2d Cir.1970) ("It is surely of some significance in deciding whether an agreement contains an implied obligation that the party so arguing tried to make the obligation explicit and failed").

The district court's recognition of an implied license is also inconsistent with the negotiating history regarding [redacted] During the parties' negotiations, Roxane

pushed for broad license rights, while Endo pushed for narrower license rights. Once the parties reached agreement on the scope of the patents licensed, as memorialized in the agreed-upon term sheet, Endo included [redacted]

c. THE DISTRICT COURT'S RECOGNITION OF AN IMPLIED LICENSE IS EXCEEDINGLY INEQUITABLE UNDER THE CIRCUMSTANCES

Moreover, the district court's recognition of an implied license is exceedingly inequitable under the circumstances presented. Roxane bases its license defense on the supposed relationship and similarities between the '122 and '216 patents at issue here and the '250 patent that was included within the scope of the patents licensed under the Agreement. However, the '122 and '216 patents are quite different from the '250 patent, as evidenced by the fact that Endo did not even assert the '250 patent against Roxane in the prior litigation, while it is undisputed that Roxane's tablets infringe the '122 and '216 patents. Endo was content to grant a covenant on the '250 patent because Roxane did not infringe the patent. It makes no sense to extend that covenant by implication into a blanket license to any and all patents that actually do cover Roxane's tablets.

Indeed, Endo is being punished here for doing the right thing. Endo's promise here with respect to the '250 patent was not to assert the patent—which requires xantham gum, locust bean gum and other ingredients—against the Roxane ANDA tablets which did not include any of those ingredients. In other words, Endo promised not to violate Rule 11 by filing a frivolous lawsuit. The context was the settlement of a Hatch-Waxman Act ANDA case in which the '250 patent was not at issue and admittedly not infringed. The patent was included in the settlement only because it was listed on the Orange Book, and it is customary in these circumstances to resolve all issues regarding such listed patents, as the Hatch-Waxman Act authorizes generic manufacturers to file declaratory judgment actions concerning patents that are listed in the Orange Book but not asserted by the branded pharmaceutical company. *See* 21 U.S.C. § 355(j)(5)(C). If this Court were to rule that granting a covenant on a non-infringing product with respect to an unasserted Orange Book-listed patent estops the patentee as a matter of law from subsequently asserting of any and all patents that might issue it at any time in the future, that would upset the settled expectations of parties to hundreds, if not thousands, of license agreements. While it might be inequitable to allow a patent holder to assert a later-issued continuation patent that is essentially identical to a licensed patent, that is a far cry from the circumstances here. The party trying to take unfair advantage of the situation is Roxane, not Endo.

That is particularly so because the only patent Endo asserted in the prior litigation (the '456 patent) expired in September 2013, while the patents now in suit do not expire until 2023 (the '122 and '216 patents) and 2029 (the '482 patent), at the earliest. (JA04869 at ¶¶ 49, 51). Accordingly, the district court's recognition of an implied license has the effect of converting the express right to launch a mere two months before the only asserted patent expired (FDA approved Roxane's ANDA in July 2013), into licenses that extend through 2029. The value of the implied rights—***up to 16 years of royalty-free infringement of three patents***—would dwarf the value of the express rights for which they actually negotiated—***two months of royalty-free infringement of a single patent***. Endo would have been far better off if it had gone to trial and lost the underlying litigation, rather than settling and being deemed by judicial fiat to have lost its right to enforce three later-issued and later-expiring patents.

3. THE CASES ON WHICH ROXANE RELIES ARE READILY DISTINGUISHABLE

Roxane bases its implied license defense primarily on *TransCore* and *General Protecht*. Those cases, however, are factually distinguishable.

TransCore involved a manufacturer of toll collection systems that sued a competitor for infringement of a number of patents; and in settling that litigation, covenanted not to sue the manufacturer for future infringement of those patents. 563 F.3d at 1274. Thereafter, TransCore sued one of the competitors' customers

for infringement of three of the patents included in that covenant, as well as a related fourth patent (referred to as the '946 patent), that was a continuation of one of the other three patents at issue (referred to as the '082 patent), but which had not yet issued at the time of the settlement. *See id.* (*See also* JA05199). Based on the '946 patent's relationship to the covenanted patents, and its finding that "TransCore's later-issued '946 patent was 'broader than, and necessary to practice, at least the [covenanted] '082 patent,'" this Court held that the competitor and its customers had an implied license to the '946 patent. 563 F.3d at 1279.

General Protecht presented a similar situation, and the Court re-affirmed that "from [its] holding in *TransCore* it reasonably follows that where, as here, ***continuations issue from parent patents that previously have been licensed*** as to certain products, it may be presumed that, absent a clear indication of mutual intent to the contrary, those products are impliedly licensed under the continuations as well." 651 F.3d at 1362 (emphasis added).

Those cases are distinguishable for a variety of reasons. First, the holdings and the reasoning of those cases are both limited to circumstances in which the allegedly impliedly licensed patent is a continuation of an expressly licensed patent, and the products at issue ***infringe both the old and new patents***. As this court later explained, *TransCore* and *General Protecht* addressed the concern that allowing a patentee "to sue on subsequent patents, when those later patents contain

the same subject matter that was licensed, risks derogating rights for which the licensee has paid consideration." *Intel v. Negotiated Data Solutions*, 703 F.3d 1360, 1366 (Fed. Cir. 2012). The continuation patent in *TransCore* had the same specification as the licensed patent. The same was true in *General Protecht*. In *Intel*, the licensor tried to claim that a license covering a patent did not cover a reissue thereof, even though it claimed the same invention.

The bedrock principle underlying the cases Roxane cites is that one cannot license patent A, obtain a continuation or reissue patent B which has essentially the same scope, and then assert patent B— unless there is sufficient evidence that that was the true intent of the parties. Neither of those circumstances is present here. None the patents-in-suit are a continuation of any expressly licensed patent. The '122 and '216 patents are so different from the '250 patent that the parties agree that the '250 patent is not infringed and that the other two are infringed.

Moreover, *General Protecht* specifically noted that a license should not be implied where there is a clear indication of an intent to the contrary. 651 F.3d at 1361-62. Here, as is described in detail above, both the express terms of the parties' Agreement and the undisputed evidence concerning the parties' negotiating history demonstrate clearly and unequivocally that the parties did not intend to grant Roxane a license under the patents-in-suit. Roxane sought but failed to include within the scope of patents expressly licensed under the

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Agreement [redacted]

Finally, *TransCore* and *General Protecht* are based on equitable considerations, and as is discussed above, recognizing an implied license under the circumstances presented here would be highly inequitable. The district court's failure to look into the equities, which it felt would have required a "substantial hearing" or a "full trial" (Ex. 11 at 48), was clear error and therefore an abuse of discretion.

[11] In *TransCore*, the agreement included a provision stating that the covenant "shall not apply to any other patents . . . to be issued in the future." The court found that that provision was not inconsistent with finding an implied license in the circumstances presented, because although it might preclude a claim that *all* future patents are impliedly licensed, it is not contrary to finding an implied license to continuations of the specifically listed patents. 563 F.3d at 1279. Here, [redacted]

C. THE COURT SHOULD REMAND THE MATTER TO THE DISTRICT COURT FOR PROPER CONSIDERATION OF ENDO'S MOTION

For all of the above reasons, the Court should reverse the district court's ruling denying Endo's motion for a preliminary injunction. Because the district court denied the motion without having considered Endo's evidence of irreparable harm, or the other traditional injunction factors, the Court should remand the matter back to the district court with instructions that Endo is likely to succeed with respect to Roxane's license defenses, and for proper consideration of Endo's motion in view of the mandate from this Court.

VIII. CONCLUSION

For the foregoing reasons, Endo respectfully requests that the Court reverse the district court's denial of Endo's motion for a preliminary injunction and remand to the district court for full consideration of Endo's motion on the merits.

Date: October 2, 2013

Respectfully submitted,

By: /s/ Martin J. Black

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ADDENDUM

ADDENDUM

TABLE OF CONTENTS

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

ENDO PHARMACEUTICALS INC., Plaintiff, v. ACTAVIS INC. and ACTAVIS SOUTH ATLANTIC LLC, Defendants.	C.A. No. 12-cv-8985-TPG
ENDO PHARMACEUTICALS INC., Plaintiff, v. ROXANE LABORATORIES, INC., Defendants.	C.A. No. 13-cv-3288 (TPG)

ORDER DENYING PLAINTIFF'S MOTION FOR PRELIMINARY INJUNCTION

THIS MATTER having been brought before the Court by plaintiff Endo Pharmaceuticals Inc. upon motions pursuant to Fed. R. Civ. P. 65 for a preliminary injunction in each of the above-captioned cases, seeking to enjoin defendants Actavis Inc. and Actavis South Atlantic LLC (collectively, "Actavis") (in the 12-cv-8985 action) and defendant Roxane Laboratories, Inc. (in the 13-cv-3288 action) from marketing or selling their respective generic oxymorphone extended release tablets approved under, respectively, Abbreviated New Drug Application Nos. 79-046 (Actavis) and 20-0822 (Roxane), in each instance pending a trial on the merits of Endo's patent infringement claims; and the Court having considered the papers submitted by the parties in connection with those motions, and the oral arguments of counsel presented on August 26, 2013 and September 12, 2013; and good cause appearing,

IT IS on this 18 day of September, 2013,

HEREBY ORDERED THAT, for the reasons set forth on the record on September 12, 2013, Endo's motions for a preliminary injunction are hereby DENIED.

IT IS FURTHER ORDERED THAT, upon consideration of the arguments of counsel, Endo's oral motion pursuant to Fed. R. Civ. P. 62(c) for entry of an injunction pending an appeal of the order denying Endo's motions for a preliminary injunction is hereby DENIED.

Dated: Sept. 18, 2013

Thomas P. Griesa

HONORABLE THOMAS P. GRIESA
UNITED STATES DISTRICT JUDGE

US007851482B2

(12) **United States Patent**
Dung et al.

(10) **Patent No.: US 7,851,482 B2**
(45) **Date of Patent: Dec. 14, 2010**

(54) **METHOD FOR MAKING ANALGESICS**

(75) Inventors: **Jen-Sen Dung**, Boothwyn, PA (US); **Erno M. Keskeny**, Wilmington, DE (US); **James J. Mencel**, North Wales, PA (US)

(73) Assignee: **Johnson Matthey Public Limited Compnay**, London (GB)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 646 days.

(21) Appl. No.: **11/866,840**

(22) Filed: **Oct. 3, 2007**

(65) **Prior Publication Data**

US 2008/0146601 A1 Jun. 19, 2008

(30) **Foreign Application Priority Data**

Dec. 14, 2006 (GB) 0624880.1

(51) **Int. Cl.**
A61K 31/485 (2006.01)
C07D 489/04 (2006.01)

(52) **U.S. Cl.** **514/282**; 546/45; 546/44

(58) **Field of Classification Search** 514/282; 546/45, 44

See application file for complete search history.

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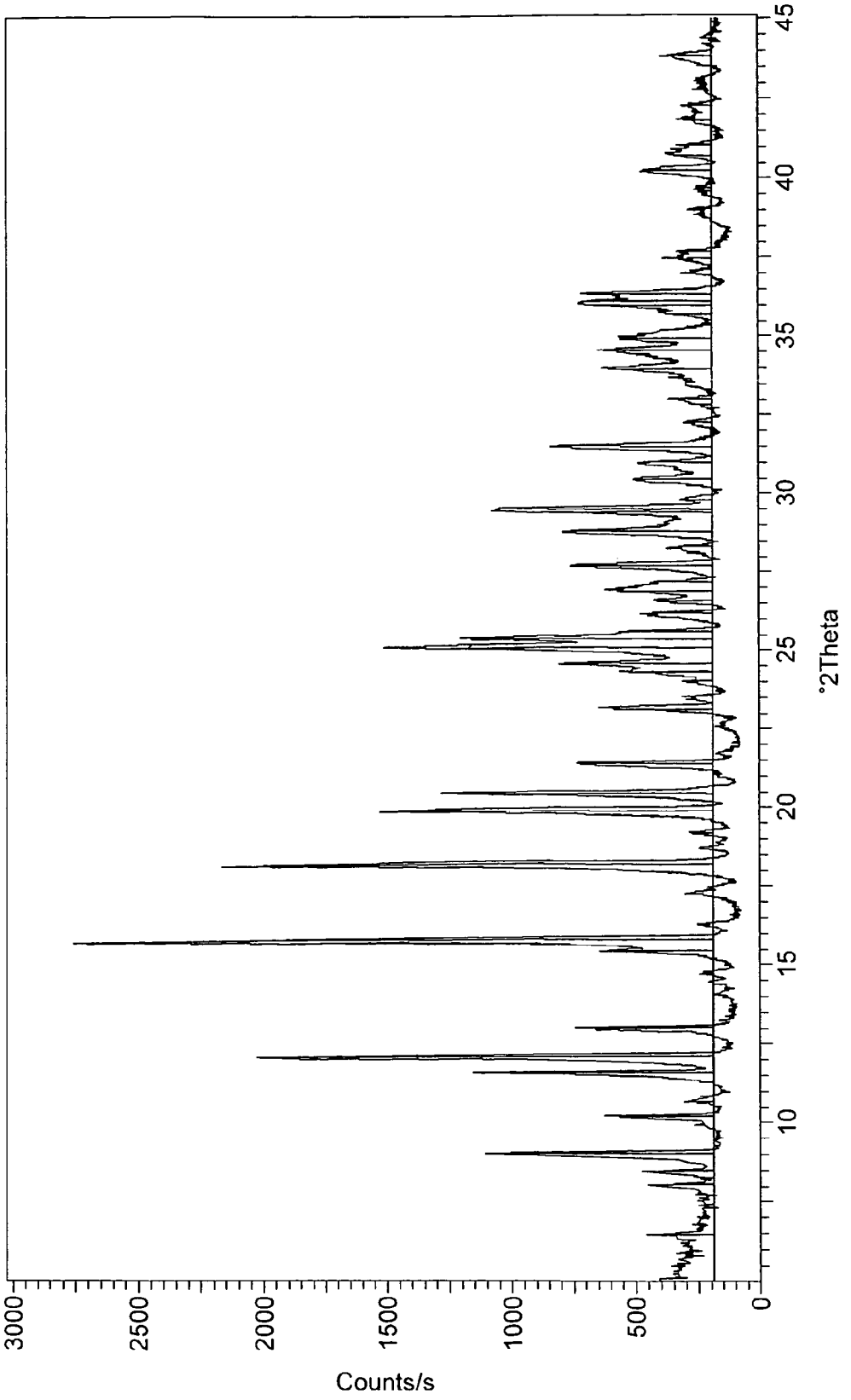
Primary Examiner Charanjit S Aulakh
(74) *Attorney, Agent, or Firm*—RatnerPrestia

(57) **ABSTRACT**

Improved analgesic oxymorphone hydrochloride contains less than 10 ppm of alpha, beta unsaturated ketones and pharmaceutical preparations comprising such oxymorphone hydrochloride. The oxymorphone hydrochloride is produced by reducing a starting material oxymorphone hydrochloride using gaseous hydrogen and under specified acidity, solvent system and temperature conditions. A specific polymorph of oxymorphone hydrochloride may be obtained by hydration.

21 Claims, 1 Drawing Sheet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METHOD FOR MAKING ANALGESICS

FIELD OF THE INVENTION

This invention concerns an improved method for making analgesics, more especially for making the opiate oxymorphone as its hydrochloride.

BACKGROUND OF THE INVENTION

Oxymorphone, generally administered in the form of its hydrochloride salt, is a potent semi-synthetic opiate analgesic, for the relief of moderate to severe pain, and has been approved for use since 1959. It can be administered as an injectable solution, suppository, tablet or extended release tablet. It is desirable to develop high purity forms of oxymorphone and a method for its synthesis.

Several methods for synthesising oxymorphone from compounds isolated from the opium poppy or compounds derived therefrom are known, for example, starting from morphine, thebaine, or from oxycodone. There remains the need for methods which permit the formation of oxymorphone with low contamination of alpha, beta unsaturated ketones. The present invention provides an improved oxymorphone product and a method for producing such oxymorphone.

U.S. Pat. No. 7,129,248 claims a process for producing oxycodone hydrochloride with less than 25 ppm of 14-hydroxycodeinone, by hydrogenating oxycodone having greater than 100 ppm 14-hydroxycodeinone. The synthetic route to oxycodone taught in US'248 starts from thebaine and produces 14-hydroxycodeinone as an intermediate product and 8,14-dihydroxy-7,8-dihydrocodeinone as a by-product resulting from over-oxidation of thebaine. During conversion of oxycodone free base to the hydrogen chloride salt, the by-product may undergo acid-catalysed dehydration and be converted into 14-hydroxycodeinone. Thus the final oxycodone hydrogen chloride salt contains unreacted 14-hydroxycodeinone as well as 14-hydroxycodeinone derived from the by-product 8,14-dihydroxy-7,8-dihydrocodeinone. A hydrogenation step is claimed to reduce contents of 14-hydroxycodeinone from at least 100 ppm to less than 25 ppm.

SUMMARY OF THE INVENTION

The present invention provides an oxymorphone hydrochloride product containing less than 10 ppm of alpha, beta unsaturated ketones.

The invention also provides a method of purifying oxymorphone hydrochloride to yield an oxymorphone hydrochloride product containing less than 10 ppm of alpha, beta unsaturated ketones, which method comprises reducing a starting material oxymorphone hydrochloride in a strongly acid water and alcohol solvent, using gaseous hydrogen at a temperature in the range from 60 to 70° C. Reduction is suitably carried out for a period of at least 20 hours, but in another embodiment, reduction is carried out for 1 to 20 hours.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will be described below with reference to the drawing, in which:

FIG. **1** is the Powder X-Ray Diffraction pattern collected for a hydrated oxymorphone hydrochloride product made according to Example 3.2D.

DETAILED DESCRIPTION OF THE INVENTION

Preferably, the solvent is ethanol/water, although other water miscible alcohols, such as isopropanol and n-propanol, may be used. The reaction medium is very acidic, preferably by incorporating at least two equivalents of hydrochloric acid. A pH of less than 1 is desirable.

The reaction temperature is most preferably maintained at about 65° C. Hydrogen is conveniently supplied to the reaction vessel at 2.41 bar pressure.

The method of the invention has been able to reduce starting material oxymorphone hydrochloride having very high (of the order of 0.3 to 0.5%, or 3,000 to 5,000 ppm) content of alpha, beta unsaturated ketones to less than 10 ppm, and in many cases to undetectable levels (by HPLC).

The starting material oxymorphone hydrochloride may be an isolated or non-isolated material. Desirably, it has been obtained by the formation of the hydrogen chloride salt by heating oxymorphone free base in the presence of hydrochloric acid and an alcohol/water reaction medium. Suitable temperatures are 60-70° C. It can be seen that the reaction medium is ideal for the reduction of the method of the invention, so that it is generally not necessary to isolate the oxymorphone hydrochloride. However, the starting material oxymorphone hydrochloride may be isolated from the reaction medium or may be from another source.

The oxymorphone free base is itself preferably prepared by a reduction of 14-hydroxymorphinone. This may be carried out in a single- or two-stage process. The reduction is preferably carried out in acetic acid using gaseous hydrogen and a palladium on carbon catalyst. Preferred temperatures are of the order of 30° C. The base is precipitated by adding aqueous ammonia (NH_4OH).

This reduction may be in the presence of the reaction medium to which is added dichloromethane in methanol, Florasil and n-propanol.

The 14-hydroxymorphinone itself is most suitably prepared by hydroxylation of oripavine, using hydrogen peroxide in the presence of formic acid.

Oripavine is a known compound, which is extractable from poppy straw. The strain developed in Tasmania to be a high-Thebaine-yielding strain also produces higher than normal levels of oripavine.

The process of the invention is highly flexible, permitting many reaction steps to be carried out without isolation of intermediate products, whilst still retaining high (of the order of 50%) overall yields from oripavine, as well as remarkably high purity. Under favourable conditions, the presence of alpha, beta unsaturated ketones is undetectable by conventional means such as HPLC, but the skilled person can readily achieve less than 10 ppm contamination. The process of the invention has been successfully carried out at kilogram scale.

The oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones can be incorporated into pharmaceutical dosage forms, e.g., by admixtures of the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones with conventional excipients, i.e., pharmaceutically acceptable organic or inorganic carrier substances. For oral formulations, the dosage forms can provide a sustained release of the active component. Suitable pharmaceutically acceptable carriers include but are not limited to, alcohols, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols, gelate, carbohydrates such as lactose, amylose or starch, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxy-methylcellulose, polyvinylpyrrolidone, etc. The pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, disintegrants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure buffers, colouring, flavouring and/or aro-

matic substances and the like. The compositions intended for oral use may be prepared according to any method known in the art and such compositions may contain one or more agents selected from the group consisting of inert, non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. Such excipients include, for example an inert diluent such as lactose; granulating and disintegrating agents such as cornstarch; binding agents such as starch; and lubricating agents such as magnesium stearate. The tablets may be uncoated or they may be coated by known techniques for elegance or to delay release of the active ingredients. Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert diluent. The oral dosage forms of the present invention may be in the form of tablets (sustained release and/or immediate release), troches, lozenges, powders or granules, hard or soft capsules, microparticles (e.g., microcapsules, microspheres and the like), buccal tablets, solutions, suspensions, etc.

In certain embodiments, the present invention provides for a method of treating pain by administering to a human patient the dosage forms described herein.

When the dosage form is oral, the dosage form of the present invention contains from about 1 mg to about 40 mg of oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones. Particularly preferred dosages are about 5 mg, about 10 mg, about 20 mg or about 40 mg however other dosages may be used as well. The oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones can also be formulated with suitable pharmaceutically acceptable excipients to provide a sustained release of having less than 10 ppm of alpha, beta unsaturated ketones. Such formulations can be prepared in accordance with US 2003/129230 A1, US 2003/129234 A1 and US 2003/157167 A1.

The oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones can be formulated as a sustained release oral formulation in any suitable tablet, coated tablet or multiparticulate formulation known to those skilled in the art. The sustained release dosage form may include a sustained release material that is incorporated into a matrix along with the oxymorphone salt thereof.

The sustained release dosage form may optionally comprise particles containing oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones. In certain embodiments, the particles have a diameter from about 0.1 mm to about 2.5 mm, preferably from about 0.5 mm to about 2 mm. Preferably, the particles are film coated with a material that permits release of the active at a sustained rate in an aqueous medium. The film coat is chosen so as to achieve, in combination with the other stated properties, desired release properties. The sustained release coating formulations of the present invention should preferably be capable of producing a strong, continuous film that is smooth and elegant, capable of supporting pigments and other coating additives, non-toxic, inert, and tack-free.

Coated Beads

In certain embodiments of the present invention a hydrophobic material is used to coat inert pharmaceutical beads such as nu pariel 18/20 beads, and a plurality of the resultant solid sustained release beads may thereafter be placed in a gelatin capsule in an amount sufficient to provide an effective sustained release dose when ingested and contacted by an environmental fluid, e.g., gastric fluid or dissolution media.

The sustained release bead formulations of the present invention slowly release the active component of the present invention, e.g., when ingested and exposed to gastric fluids, and then to intestinal fluids. The sustained release profile of the formulations of the invention can be altered, for example, by varying the amount of overcoating with the hydrophobic material, altering the manner in which a plasticiser is added to the hydrophobic material, by varying the amount of plasticiser relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc. The dissolution profile of the ultimate product may also be modified, for example, by increasing or decreasing the thickness of the retardant coating.

Spheroids or beads coated with the agent(s) of the present are prepared, e.g., by dissolving the agent(s) in water and then spraying the solution onto a substrate, for example, nu pariel 18/20 beads, using a Wuster insert. Optionally, additional ingredients are also added prior to coating the beads in order to assist the binding of the active to the beads, and/or to color the solution, etc. For example, a product that includes hydroxypropylmethylcellulose, etc with or without colorant (e.g., Opadry™, commercially available from Colorcon, Inc.) may be added to the solution and the solution mixed (e.g., for about 1 hour) prior to application of the same onto the beads. The resultant coated substrate, in these example beads, may then be optionally overcoated with a barrier agent, to separate the active component(s) from the hydrophobic sustained release coating. An example of a suitable barrier agent is one which comprises hydroxypropylmethylcellulose. However, any film-former known in the art may be used. It is preferred that the barrier agent does not affect the dissolution rate of the final product.

The beads may then be overcoated with an aqueous dispersion of the hydrophobic material. The aqueous dispersion of hydrophobic material preferably further includes an effective amount of plasticiser, e.g. triethyl citrate. Pre-formulated aqueous dispersions of ethylcellulose, such as Aquacoat™ or Surelease™, may be used. If Surelease™ is used, it is not necessary to separately add a plasticiser. Alternatively, pre-formulated aqueous dispersions of acrylic polymers such as Eudragit™ can be used.

The coating solutions of the present invention preferably contain, in addition to the film-former, plasticiser, and solvent system (i.e., water), a colorant to provide elegance and product distinction. Colour may be added to the solution of the therapeutically active agent instead, or in addition to the aqueous dispersion of hydrophobic material. For example, colour may be added to Aquacoat™ via the use of alcohol or propylene glycol based colour dispersions, milled aluminium lakes and opacifiers such as titanium dioxide by adding colour with shear to water soluble polymer solution and then using low shear to the plasticised Aquacoat™. Alternatively, any suitable method of providing colour to the formulations of the present invention may be used. Suitable ingredients for providing colour to the formulation when an aqueous dispersion of an acrylic polymer is used include titanium dioxide and colour pigments, such as iron oxide pigments. The incorporation of pigments, may, however, increase the retard effect of the coating.

Plasticised hydrophobic material may be applied onto the substrate comprising the agent(s) by spraying using any suitable spray equipment known in the art. In a preferred method, a Wurster fluidised-bed system is used in which an air jet, injected from underneath, fluidizes the core material and effects drying while the acrylic polymer coating is sprayed on. A sufficient amount of the hydrophobic material to obtain a predetermined sustained release of the agent(s) when the coated substrate is exposed to aqueous solutions, e.g. gastric fluid, may be applied. After coating with the hydrophobic

material, a further overcoat of a film-former, such as Opadry™, is optionally applied to the beads. This overcoat is provided, if at all, in order to substantially reduce agglomeration of the beads.

The release of the agent(s) from the sustained release formulation of the present invention can be further influenced, i.e., adjusted to a desired rate, by the addition of one or more release-modifying agents, or by providing one or more passageways through the coating. The ratio of hydrophobic material to water soluble material is determined by, among other factors, the release rate required and the solubility characteristics of the materials selected.

The release-modifying agents, which function as pore-formers may be organic or inorganic, and include materials that can be dissolved, extracted or leached from the coating in an environment of use. The pore-formers may comprise one or more hydrophilic materials such as hydroxypropylmethylcellulose.

The sustained release coatings of the present invention can also include erosion-promoting agents such as starch and gums.

The sustained release coatings of the present invention can also include materials useful for making microporous lamina in the environment of use, such as polycarbonates comprised of linear polyesters of carbonic acid in which carbonate groups reoccur in the polymer chain.

The release-modifying agent may also comprise a semi-permeable polymer.

In certain preferred embodiments, the release-modifying agent is selected from hydroxypropylmethylcellulose, lactose, metal stearates, and mixtures of any of the foregoing.

The sustained release coatings of the present invention may also include an exit means comprising at least one passageway, orifice, or the like. The passageway may be formed by such methods as those disclosed in U.S. Pat. No. 3,845,770, U.S. Pat. No. 3,916,899, U.S. Pat. No. 4,063,064 and U.S. Pat. No. 4,088,864.

Matrix Formulations

In other embodiments of the present invention, the sustained release formulation is achieved via a matrix optionally having a sustained release coating as set forth herein. The materials suitable for inclusion in a sustained release matrix may depend on the method used to form the matrix.

For example, a matrix in addition to the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones may include: hydrophilic and/or hydrophobic materials, such as gums, cellulose ethers, acrylic resins, protein derived materials. The list is not meant to be exclusive, any pharmaceutically acceptable hydrophobic material or hydrophilic material which is capable of imparting sustained release of the agent(s) and which melts (or softens to the extent necessary to be extruded) may be used in accordance with the present invention.

Digestible, long chain (C_8-C_{50}, especially C_{12}-C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and waxes, and stearyl alcohol; and polyalkylene glycols. Of these polymers, acrylic polymers, especially Eudragit™. RSPO—the cellulose ethers, especially hydroxyalkylcelluloses and carboxyalkylcelluloses, are preferred. The oral dosage form may contain between 1% and 80% (by weight) of at least one hydrophilic or hydrophobic material.

When the hydrophobic material is a hydrocarbon, the hydrocarbon preferably has a melting point of between 25° C. and 90° C. Of the long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred. The oral dosage form may contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon.

Preferably, the oral dosage form contains up to 60% (by weight) of at least one polyalkylene glycol.

The hydrophobic material is preferably selected from the group consisting of alkylcelluloses, acrylic and methacrylic acid polymers and copolymers, shellac, zein, hydrogenated castor oil, hydrogenated vegetable oil, or mixtures thereof. In certain preferred embodiments of the present invention, the hydrophobic material is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer, poly(methyl methacrylate), poly (methacrylic acid) (anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers. In other embodiments, the hydrophobic material is selected from materials such as hydroxyalkylcelluloses such as hydroxypropylmethylcellulose and mixtures of the foregoing.

Preferred hydrophobic materials are water-insoluble with more or less pronounced hydrophilic and/or hydrophobic trends. Preferably, the hydrophobic materials useful in the invention have a melting point from about 25° C. to about 200° C., preferably from about 45° C. to about 90° C. Specifically, the hydrophobic material may comprise natural or synthetic waxes, fatty alcohols (such as lauryl, myristyl, stearyl, cetyl or preferably cetostearyl alcohol), fatty acids, including but not limited to fatty acid esters, fatty acid glycerides (mono-, di-, and tri-glycerides), hydrogenated fats, hydrocarbons, normal waxes, stearic aid, stearyl alcohol and hydrophobic and hydrophilic materials having hydrocarbon backbones. Suitable waxes include, for example, beeswax, glycowax, castor wax and carnauba wax. For the purposes of the present invention, a wax-like substance is defined as any material that is normally solid at room temperature and has a melting point of from about 25° C. to about 100° C.

Suitable hydrophobic materials which may be used in accordance with the present invention include digestible, long chain (C_8-C_{50}, especially C_{12}-C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and natural and synthetic waxes. Hydrocarbons having a melting point of between 25° C. and 90° C. are preferred. Of the long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred in certain embodiments. The oral dosage form may contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon. Preferably, a combination of two or more hydrophobic materials are included in the matrix formulations. If an additional hydrophobic material is included, it is preferably selected from natural and synthetic waxes, fatty acids, fatty alcohols, and mixtures of the same. Examples include beeswax, carnauba wax, stearic acid and stearyl alcohol. This list is not meant to be exclusive.

One particular suitable matrix comprises at least one water soluble hydroxyalkyl cellulose, at least one C_{12}-C_{36}, preferably C_{14}-C_{22}, aliphatic alcohol and, optionally, at least one polyalkylene glycol. The at least one hydroxyalkyl cellulose is preferably a hydroxy (C_1 to C_6) alkyl cellulose, such as hydroxypropylcellulose, hydroxypropyl-methylcellulose and, especially, hydroxyethylcellulose. The amount of the at least one hydroxyalkyl cellulose in the present oral dosage form will be determined, inter alia, by the precise rate of oxymorphone hydrochloride release required. The at least

one aliphatic alcohol may be, for example, lauryl alcohol, myristyl alcohol or stearyl alcohol. In particularly preferred embodiments of the present oral dosage form, however, the at least one aliphatic alcohol is cetyl alcohol or cetostearyl alcohol. The amount of the at least one aliphatic alcohol in the present oral dosage form will be determined, as above, by the precise rate of opioidoxycmorphone release required. It will also depend on whether at least one polyalkylene glycol is present in or absent from the oral dosage form. In the absence of at least one polyalkylene glycol, the oral dosage form preferably contains between 20% and 50% (by wt) of the at least one aliphatic alcohol. When at least one polyalkylene glycol is present in the oral dosage form, then the combined weight of the at least one aliphatic alcohol and the at least one polyalkylene glycol preferably constitutes between 20% and 50% (by wt) of the total dosage.

In one embodiment, the ratio of, e.g., the at least one hydroxyalkyl cellulose or acrylic resin to the at least one aliphatic alcohol/polyalkylene glycol determines, to a (w/w) of the at least one hydroxyalkyl cellulose to the at least one aliphatic alcohol/polyalkylene glycol of between 1:2 and 1:4 is preferred, with a ratio of between 1:3 and 1:4 being particularly preferred.

The at least one polyalkylene glycol may be, for example, polypropylene glycol or, preferably, polyethylene glycol. The number average molecular weight of the at least one polyalkylene glycol is preferably between 1,000 and 15,000 especially between 1,500 and 12,000.

Another suitable sustained release matrix would comprise an alkylcellulose (especially ethyl cellulose), a C_{12} to C_{36} aliphatic alcohol and, optionally, a polyalkylene glycol.

In another preferred embodiment, the matrix includes a pharmaceutically acceptable combination of at least two hydrophobic materials.

In addition to the above ingredients, a sustained release matrix may also contain suitable quantities of other materials, e.g. diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art.

Matrix—Particulates

In order to facilitate the preparation of a solid, sustained release, oral dosage form according to this invention, any method of preparing a matrix formulation known to those skilled in the art may be used. For example incorporation in the matrix may be effected, for example, by (a) forming granules comprising at least one water soluble hydroxyalkyl cellulose, and the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones; (b) mixing the hydroxyalkyl cellulose containing granules with at least one C_{12} to C_{36} aliphatic alcohol; and (c) optionally, compressing and shaping the granules. Preferably, the granules are formed by wet granulating the hydroxalkyl cellulose granules with water.

In yet other alternative embodiments, a spheronizing agent, together with the active component can be spheronized to form spheroids. Microcrystalline cellulose is a preferred spheronizing agent. A suitable microcrystalline cellulose is, for example, the material sold as Avicel PH 101 (Trade Mark, FMC Corporation). In such embodiments, in addition to the active ingredient and spheronizing agent, the spheroids may also contain a binder. Suitable binders, such as low viscosity, water soluble polymers, will be well known to those skilled in the pharmaceutical art. However, water soluble hydroxy lower alkyl cellulose, such as hydroxypropyl-cellulose, are preferred. Additionally (or alternatively) the spheroids may contain a water insoluble polymer, especially an acrylic polymer, an acrylic copolymer, such as a methacrylic acid-ethyl acrylate copolymer, or ethyl cellulose. In such embodiments, the sustained release coating will generally include a hydrophobic material such as (a) a wax, either alone or in admixture with a fatty alcohol; or (b) shellac or zein.

Melt Extrusion Matrix

Sustained release matrices can also be prepared via melt-granulation or melt-extrusion techniques. Generally, melt-granulation techniques involve melting a normally solid hydrophobic material, e.g. a wax, and incorporating a powdered drug therein. To obtain a sustained release dosage form, it may be necessary to incorporate an additional hydrophobic substance, e.g. ethylcellulose or a water-insoluble acrylic polymer, into the molten wax hydrophobic material. Examples of sustained release formulations prepared via melt-granulation techniques are found in U.S. Pat. No. 4,861,598.

The additional hydrophobic material may comprise one or more water-insoluble wax-like thermoplastic substances possibly mixed with one or more wax-like thermoplastic substances being less hydrophobic than said one or more water-insoluble wax-like substances. In order to achieve constant release, the individual wax-like substances in the formulation should be substantially non-degradable and insoluble in gastrointestinal fluids during the initial release phases. Useful water-insoluble wax-like substances may be those with a water-solubility that is lower than about 1:5,000 (w/w).

In addition to the above ingredients, a sustained release matrix may also contain suitable quantities of other materials, e.g., diluents, lubricants, binders, granulating aids, colourants, flavourants and glidants that are conventional in the pharmaceutical art. The quantities of these additional materials will be sufficient to provide the desired effect to the desired formulation.

In addition to the above ingredients, a sustained release matrix incorporating melt-extruded multiparticulates may also contain suitable quantities of other materials, e.g. diluents, lubricants, binders, granulating aids, colourants, flavourants and glidants that are conventional in the pharmaceutical art in amounts up to about 50% by weight of the particulate if desired.

Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms are described in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (1986).

Melt Extrusion Multiparticulates

The preparation of a suitable melt-extruded matrix according to the present invention may, for example, include the steps of blending the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones together with at least one hydrophobic material and preferably the additional hydrophobic material to obtain a homogeneous mixture. The homogeneous mixture is then heated to a temperature sufficient to at least soften the mixture sufficiently to extrude the same. The resulting homogeneous mixture is then extruded to form strands. The extrudate is preferably cooled and cut into multiparticulates by any means known in the art. The strands are cooled and cut into multiparticulates. The multiparticulates are then divided into unit doses. The extrudate preferably has a diameter of from about 0.1 mm to about 5 mm and provides sustained release of the therapeutically active agent for a time period of from about 8 hours to about 24 hours.

An optional process for preparing the melt extrusions of the present invention includes directly metering into an extruder a hydrophobic material, the oxymorphone hydrochloride

having less than 10 ppm of alpha, beta unsaturated ketones, and an optional binder; heating the homogenous mixture; extruding the homogenous mixture to thereby form strands; cooling the strands containing the homogeneous mixture; cutting the strands into particles having a size from about 0.1 mm to about 12 mm; and dividing said particles into unit doses. In this aspect of the invention, a relatively continuous manufacturing procedure is realized.

The diameter of the extruder aperture or exit port can also be adjusted to vary the thickness of the extruded strands. Furthermore, the exit part of the extruder need not be round; it can be oblong, rectangular, etc. The exiting strands can be reduced to particles using a hot wire cutter, guillotine, etc.

The melt extruded multiparticulate system can be, for example, in the form of granules, spheroids or pellets depending upon the extruder exit orifice. For the purposes of the present invention, the terms "melt-extruded multiparticulate(s)" and "melt-extruded multiparticulate system(s)" and "melt-extruded particles" shall refer to a plurality of units, preferably within a range of similar size and/or shape and containing one or more active agents and one or more excipients, preferably including a hydrophobic material as described herein. In this regard, the melt-extruded multiparticulates will be of a range of from about 0.1 mm to about 12 mm in length and have a diameter of from about 0.1 mm to about 5 mm. In addition, it is to be understood that the melt-extruded multiparticulates can be any geometrical shape within this size range. Alternatively, the extrudate may simply be cut into desired lengths and divided into unit doses of the therapeutically active agent without the need of a spheronization step.

In one preferred embodiment, oral dosage forms are prepared to include an effective amount of melt-extruded multiparticulates within a capsule. For example, a plurality of the melt-extruded multiparticulates may be placed in a gelatin capsule in an amount sufficient to provide an effective sustained release dose when ingested and contacted by gastric fluid.

In another preferred embodiment, a suitable amount of the multiparticulate extrudate is compressed into an oral tablet using conventional tabletting equipment using standard techniques. Techniques and compositions for making tablets (compressed and moulded), capsules (hard and soft gelatin) and pills are also described in Remington's Pharmaceutical Sciences, (Arthur Osol, editor), 1553-1593 (1980).

In yet another preferred embodiment, the extrudate can be shaped into tablets as set forth in U.S. Pat. No. 4,957,681, described in additional detail above.

Optionally, the sustained release melt-extruded multiparticulate systems or tablets can be coated, or the gelatin capsule containing the multiparticulates can be further coated, with a sustained release coating such as the sustained release coatings described above. Such coatings preferably include a sufficient amount of hydrophobic material to obtain a weight gain level from about 2% to about 30%, although the overcoat may be greater depending upon the desired release rate, among other things.

The melt-extruded unit dosage forms of the present invention may further include combinations of melt-extruded particles before being encapsulated. Furthermore, the unit dosage forms can also include an amount of an immediate release agent for prompt release. The immediate release agent may be incorporated, e.g., as separate pellets within a gelatin capsule, or may be coated on the surface of the multiparticulates after preparation of the dosage forms (e.g., sustained release coating or matrix-based). The unit dosage forms of the present invention may also contain a combination of sustained release beads and matrix multiparticulates to achieve a desired effect.

The sustained release formulations of the present invention preferably slowly release the agent(s), e.g. when ingested and exposed to gastric fluids, and then to intestinal fluids. The sustained release profile of the melt-extruded formulations of the invention can be altered, for example, by varying the amount of retardant, i.e., hydrophobic material, by varying the amount of plasticiser relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc.

In other embodiments of the invention, the melt extruded material is prepared without the inclusion of the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones, which can be added thereafter to the extrudate. Such formulations typically will have the agents blended together with the extruded matrix material, and then the mixture would be tableted in order to provide a slow release formulation.

Coatings

The dosage forms of the present invention may optionally be coated with one or more materials suitable for the regulation of release or for the protection of the formulation. In one embodiment, coatings are provided to permit either pH-dependent or pH-independent release. A pH-dependent coating serves to release the active in desired areas of the gastrointestinal (GI) tract, e.g. the stomach or small intestine, such that an absorption profile is provided which is capable of providing at least about eight hours and preferably about twelve hours to up to about twenty-four hours of analgesia to a patient. When a pH-independent coating is desired, the coating is designed to achieve optimal release regardless of pH-changes in the environmental fluid, e.g., the GI tract. It is also possible to formulate compositions that release a portion of the dose in one desired area of the GI tract, e.g., the stomach, and release the remainder of the dose in another area of the GI tract, e.g., the small intestine.

Formulations according to the invention that utilize pH-dependent coatings to obtain formulations may also impart a repeat-action effect whereby unprotected drug is coated over the enteric coat and is released in the stomach, while the remainder, being protected by the enteric coating, is released further down the gastrointestinal tract. Coatings which are pH-dependent may be used in accordance with the present invention include shellac, cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), hydroxypropylmethylcellulose phthalate, and methacrylic acid ester copolymers, zein, and the like.

In certain preferred embodiments, the substrate (e.g., tablet core bead, matrix particle) containing the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones thereof is coated with a hydrophobic material selected from (i) an alkylcellulose; (ii) an acrylic polymer; or (iii) mixtures thereof. The coating may be applied in the form of an organic or aqueous solution or dispersion. The coating may be applied to obtain a weight gain from about 2% to about 25% of the substrate in order to obtain a desired sustained release profile. Coatings derived from aqueous dispersions are described in detail U.S. Pat. No. 5,273,760, U.S. Pat. No. 5,286,493, U.S. Pat. No. 5,324,351, U.S. Pat. No. 5,356,467, and U.S. Pat. No. 5,472,712.

Alkylcellulose Polymers

Cellulosic materials and polymers, including alkylcelluloses, provide hydrophobic materials well suited for coating the beads according to the invention. Simply by way of example, one preferred alkylcellulosic polymer is ethylcellulose,

although the artisan will appreciate that other cellulose and/or alkylcellulose polymers may be readily employed, singly or in any combination, as all or part of a hydrophobic coating according to the invention.

Acrylic Polymers

In other preferred embodiments of the present invention, the hydrophobic material comprising the sustained release coating is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art, and are described as fully polymerised copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

In order to obtain a desirable dissolution profile, it may be necessary to incorporate two or more ammonio methacrylate copolymers having differing physical properties, such as different molar ratios of the quaternary ammonium groups to the neutral (meth)acrylic esters.

Certain methacrylic acid ester-type polymers are useful for preparing pH-dependent coatings, which may be used in accordance with the present invention. For example, there are a family of copolymers synthesized from diethylaminoethyl methacrylate and other neutral methacrylic esters, also known as methacrylic acid copolymer or polymeric methacrylates, commercially available as Eudragit™ from Rohm Tech, Inc. There are several different types of Eudragit™, for example Eudragit™ E is an example of a methacrylic acid copolymer that swells and dissolves in acidic media. Eudragit™ L is a methacrylic acid copolymer which does not swell at about pH<5.7 and is soluble at about pH>6. Eudragit™ S does not swell at about pH<6.5 and is soluble at about pH>7. Eudragit™ RL and Eudragit™ RS are water swellable, and the amount of water absorbed by these polymers is pH-dependent, however, dosage forms coated with Eudragit™ RL and RS are pH-independent.

In certain preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the Tradenames Eudragit™ RL30D and Eudragit™ RS30D, respectively. Eudragit™ RL30D and Eudragit™ RS30D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit™ RL30D and 1:40 in Eudragit™ RS30D. The mean molecular weight is about 150,000. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit™ RL/RS mixtures are insoluble in water and in digestive fluids. However, coatings formed from the same are swellable and permeable in aqueous solutions and digestive fluids.

The Eudragit™ RL/RS dispersions of the present invention may be mixed together in any desired ratio in order to ultimately obtain a sustained release formulation having a desirable dissolution profile. Desirable sustained release formulations may be obtained, for instance, from a retardant coating derived from 100% Eudragit™ RL, 50% Eudragit™ RL and 50% Eudragit™ RS, or 10% Eudragit™ RL and 90% Eudragit™ RS. Of course, one skilled in the art will recognize that other acrylic polymers may also be used, such as, for example, Eudragit™ L.

Plasticizers

In embodiments of the present invention where the coating comprises an aqueous dispersion of a hydrophobic material, the inclusion of an effective amount of a plasticiser in the aqueous dispersion of hydrophobic material will further improve the physical properties of the sustained release coating. For example, because ethyl-cellulose has a relatively high glass transition temperature and does not form flexible films under normal coating conditions, it is preferable to incorporate a plasticiser into an ethylcellulose coating containing sustained release coating before using the same as a coating material. Generally, the amount of plasticiser included in a coating solution is based on the concentration of the film-former, e.g., most often from about 1 wt % to about 50 wt % of the film-former. Concentration of the plasticiser, however, can only be properly determined after careful experimentation with the particular coating solution and method of application.

Examples of suitable plasticizers for ethylcellulose include water insoluble plasticizers such as dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate, and triacetin, although it is possible that other water-insoluble plasticizers (such as acetylated monoglycerides, phthalate esters, castor oil, etc.) may be used. Triethyl citrate is an especially preferred plasticiser for the aqueous dispersions of ethyl cellulose of the present invention.

Examples of suitable plasticizers for the acrylic polymers of the present invention include, but are not limited to citric acid esters such as triethyl citrate, tributyl citrate, dibutyl phthalate, and possibly 1,2-propylene glycol. Other plasticizers that have proved to be suitable for enhancing the elasticity of the films formed from acrylic films such as Eudragit™ RL/RS lacquer solutions include polyethylene glycols, propylene glycol, diethyl phthalate, castor oil, and triacetin. Triethyl citrate is an especially preferred plasticiser for the aqueous dispersions of ethyl cellulose of the present invention.

The addition of a small amount of talc may also help reduce the tendency of the aqueous dispersion to stick during processing, and may act as a polishing agent.

Sustained Release Osmotic Dosage Form

Sustained release dosage forms according to the present invention may also be prepared as osmotic dosage formulations. The osmotic dosage forms preferably include a bilayer core comprising a drug layer (containing the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones) and a delivery or push layer, wherein the bilayer core is surrounded by a semipermeable wall and optionally having at least one passageway disposed therein.

The expression "passageway" as used for the purpose of this invention, includes aperture, orifice, bore, pore, porous element through which oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones can be pumped, diffuse or migrate through a fibre, capillary tube, porous overlay, porous insert, microporous member, or porous composition. The passageway can also include a compound that erodes or is leached from the wall in the fluid environment of use to produce at least one passageway. Representative compounds for forming a passageway include erodible poly(glycolic) acid, or poly(lactic) acid in the wall; a gelatinous filament; a water-removable poly(vinyl alcohol); leachable compounds such as fluid-removable pore-forming polysaccharides, acids, salts or oxides. A passageway can be

formed by leaching a compound from the wall, such as sorbitol, sucrose, lactose, maltose, or fructose, to form a sustained-release dimensional pore-passageway. The dosage form can be manufactured with one or more passageways in spaced-apart relation on one or more surfaces of the dosage form. A passageway and equipment for forming a passageway are disclosed in U.S. Pat. No. 3,845,770, U.S. Pat. No. 3,916,899, U.S. Pat. No. 4,063,064 and U.S. Pat. No. 4,088,864. Passageways comprising sustained-release dimensions sized, shaped and adapted as a releasing-pore formed by aqueous leaching to provide a releasing-pore of a sustained-release rate are disclosed in U.S. Pat. No. 4,200,098 and U.S. Pat. No. 4,285,987.

In certain embodiments the drug layer may also comprise at least one polymer hydrogel. The polymer hydrogel may have an average molecular weight of between about 500 and about 6,000,000. Examples of polymer hydrogels include but are not limited to a maltodextrin polymer comprising the formula $(C_6H_{12}O_5)_nH_2O$, wherein n is 3 to 7,500, and the maltodextrin polymer comprises a 500 to 1,250,000 number-average molecular weight; a poly(alkylene oxide) represented by, e.g., a poly(ethylene oxide) and a poly(propylene oxide) having a 50,000 to 750,000 weight-average molecular weight, and more specifically represented by a poly(ethylene oxide) of at least one of 100,000, 200,000, 300,000 or 400,000 weight-average molecular weights; an alkali carboxyalkylcellulose, wherein the alkali is sodium or potassium, the alkyl is methyl, ethyl, propyl, or butyl of 10,000 to 175,000 weight-average molecular weight; and a copolymer of ethylene-acrylic acid, including methacrylic and ethacrylic acid of 10,000 to 500,000 number-average molecular weight.

In certain embodiments of the present invention, the delivery or push layer comprises an osmopolymer. Examples of an osmopolymer include but are not limited to a member selected from the group consisting of a polyalkylene oxide and a carboxyalkylcellulose. The polyalkylene oxide possesses a 1,000,000 to 10,000,000 weight-average molecular weight. The polyalkylene oxide may be a member selected from the group consisting of polymethylene oxide, polyethylene oxide, polypropylene oxide, polyethylene oxide having a 1,000,000 average molecular weight, polyethylene oxide comprising a 5,000,000 average molecular weight, polyethylene oxide comprising a 7,000,000 average molecular weight, cross-linked polymethylene oxide possessing a 1,000,000 average molecular weight, and polypropylene oxide of 1,200,000 average molecular weight. Typical osmopolymer carboxyalkylcellulose comprises a member selected from the group consisting of alkali carboxyalkylcellulose, sodium carboxymethylcellulose, potassium carboxymethylcellulose, sodium carboxyethylcellulose, lithium carboxymethylcellulose, sodium carboxyethyl-cellulose, carboxyalkylhydroxyalkylcellulose, carboxymethylhydroxyethyl cellulose, carboxyethylhydroxyethylcellulose and carboxymethylhydroxypropylcellulose. The osmopolymers used for the displacement layer exhibit an osmotic pressure gradient across the semipermeable wall. The osmopolymers imbibe fluid into dosage form, thereby swelling and expanding as an osmotic hydrogel (also known as an osmogel), whereby they push the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones thereof from the osmotic dosage form.

The push layer may also include one or more osmotically effective compounds also known as osmagents and as osmotically effective solutes. They imbibe an environmental fluid, for example, from the gastrointestinal tract, into dosage form and contribute to the delivery kinetics of the displacement layer. Examples of osmotically active compounds comprise a member selected from the group consisting of osmotic salts and osmotic carbohydrates. Examples of specific osmagents include but are not limited to sodium chloride, potassium chloride, magnesium sulphate, lithium phosphate, lithium chloride, sodium phosphate, potassium sulphate, sodium sulphate, potassium phosphate, glucose, fructose and maltose.

The push layer may optionally include a hydroxypropylalkylcellulose possessing a 9,000 to 450,000 number-average molecular weight. The hydroxypropylalkyl-cellulose is represented by a member selected from the group consisting of hydroxypropylmethylcellulose, hydroxypropylethylcellulose, hydroxypropylisopropyl cellulose, hydroxypropylbutylcellulose, and hydroxypropylpentylcellulose.

The push layer optionally may comprise a non-toxic colorant or dye. Examples of colourants or dyes include but are not limited to Food and Drug Administration Colourants (FD&C), such as FD&C No. 1 blue dye, FD&C No. 4 red dye, red ferric oxide, yellow ferric oxide, titanium dioxide, carbon black, and indigo.

The push layer may also optionally comprise an antioxidant to inhibit the oxidation of ingredients. Some examples of antioxidants include but are not limited to a member selected from the group consisting of ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, a mixture of 2 and 3 tertiary-butyl-4-hydroxyanisole, butylated hydroxytoluene, sodium isoascorbate, dihydroguaretic acid, potassium sorbate, sodium bisulfate, sodium metabisulfate, sorbic acid, potassium ascorbate, vitamin E, 4-chloro-2.6-ditertiary butylphenol, alphatocopherol, and propylgallate.

In certain alternative embodiments, the dosage form comprises a homogenous core comprising oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones, a pharmaceutically acceptable polymer (e.g., polyethylene oxide), optionally a disintegrant (e.g., polyvinylpyrrolidone), optionally an absorption enhancer (e.g., a fatty acid, a surfactant, a chelating agent, a bile salt, etc). The homogenous core is surrounded by a semipermeable wall having a passageway (as defined above) for the release of the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones.

In certain embodiments, the semipermeable wall comprises a member selected from the group consisting of a cellulose ester polymer, a cellulose ether polymer and a cellulose ester-ether polymer. Representative wall polymers comprise a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono-, di- and tricellulose alkenylates, and mono-, di- and tricellulose alkinylates. The poly(cellulose) used for the present invention comprises a number-average molecular weight of 20,000 to 7,500,000.

Additional semipermeable polymers for the purpose of this invention comprise acetaldehyde dimethycellulose acetate, cellulose acetate ethylcarbamate, cellulose acetate methylcarbamate, cellulose diacetate, propylcarbamate, cellulose acetate diethylaminoacetate; semipermeable polyamide; semipermeable polyurethane; semipermeable sulfonated polystyrene; semipermeable cross-linked polymer formed by the coprecipitation of a polyanion and a polycation, semipermeable crosslinked polystyrenes, semipermeable cross-linked poly(sodium styrene sulfonate), semipermeable crosslinked poly(vinylbenzyltrimethyl ammonium chloride) and semipermeable polymers possessing a fluid permeability of 2.5×10^{-8} to 2.5×10^{-2} (cm^2/hr atm) expressed per atmosphere of hydrostatic or osmotic pressure difference across the semipermeable wall. Other polymers useful in the present

invention are known in the art including those in Handbook of Common Polymers, Scott, J. R. and W. J. Roff, 1971, CRC Press, Cleveland, Ohio.

In certain embodiments, preferably the semipermeable wall is nontoxic, inert, and it maintains its physical and chemical integrity during the dispensing life of the drug. In certain embodiments, the dosage form comprises a binder. An example of a binder includes, but is not limited to a therapeutically acceptable vinyl polymer having a 5,000 to 350,000 viscosity-average molecular weight, represented by a member selected from the group consisting of poly-n-vinylamide, poly-n-vinylacetamide, poly(vinyl pyrrolidone), also known as poly-n-vinylpyrrolidone, poly-n-vinylcaprolactone, poly-n-vinyl-5-methyl-2-pyrrolidone, and poly-n-vinyl-pyrrolidone copolymers with a member selected from the group consisting of vinyl acetate, vinyl alcohol, vinyl chloride, vinyl fluoride, vinyl butyrate, vinyl laureate, and vinyl stearate. Other binders include for example, acacia, starch, gelatin, and hydroxypropylalkylcellulose of 9,200 to 250,000 average molecular weight.

In certain embodiments, the dosage form comprises a lubricant, which may be used during the manufacture of the dosage form to prevent sticking to die wall or punch faces. Examples of lubricants include but are not limited to magnesium stearate, sodium stearate, stearic acid, calcium stearate, magnesium oleate, oleic acid, potassium oleate, caprylic acid, sodium stearyl fumarate, and magnesium palmitate.

In certain preferred embodiments, the present invention includes a therapeutic composition comprising an amount of oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones equivalent to 10 to 40 mg oxymorphone hydrochloride, 25 mg to 500 mg of poly(alkylene oxide) having a 150,000 to 500,000 average molecular weight, 1 mg to 50 mg of polyvinylpyrrolidone having a 40,000 average molecular weight, and 0 mg to about 7.5 mg of a lubricant.

Suppositories

The sustained release formulations of the present invention may be formulated as a pharmaceutical suppository for rectal administration comprising a suitable suppository base, and oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones. Preparation of sustained release suppository formulations is described in, e.g., U.S. Pat. No. 5,215,758.

Prior to absorption, the drug must be in solution. In the case of suppositories, solution must be preceded by dissolution of the suppository base, or the melting of the base and subsequent partition of the drug from the suppository base into the rectal fluid. The absorption of the drug into the body may be altered by the suppository base. Thus, the particular suppository base to be used in conjunction with a particular drug must be chosen giving consideration to the physical properties of the drug. For example, lipid-soluble drugs will not partition readily into the rectal fluid, but drugs that are only slightly soluble in the lipid base will partition readily into the rectal fluid.

Among the different factors affecting the dissolution time (or release rate) of the drugs are the surface area of the drug substance presented to the dissolution solvent medium, the pH of the solution, the solubility of the substance in the specific solvent medium, and the driving forces of the saturation concentration of dissolved materials in the solvent medium. Generally, factors affecting the absorption of drugs from suppositories administered rectally include suppository vehicle, absorption site pH, drug pKa, degree of ionisation, and lipid solubility.

The suppository base chosen should be compatible with the active of the present invention. Further, the suppository base is preferably non-toxic and non-irritating to mucous membranes, melts or dissolves in rectal fluids, and is stable during storage.

In certain preferred embodiments of the present invention for both water-soluble and water-insoluble drugs, the suppository base comprises a fatty acid wax selected from the group consisting of mono-, di- and triglycerides of saturated, natural fatty acids of the chain length C_{12} to C_{18}.

In preparing the suppositories of the present invention other excipients may be used. For example, a wax may be used to form the proper shape for administration via the rectal route. This system can also be used without wax, but with the addition of diluent filled in a gelatin capsule for both rectal and oral administration.

Examples of suitable commercially available mono-, di- and triglycerides include saturated natural fatty acids of the 12-18 carbon atom chain sold under the trade name Novata™ (types AB, AB, B, BC, BD, BBC, E, BCF, C, D and 299), manufactured by Henkel, and Witepsol™ (types H5, H12, H15, H175, H185, H19, H32, H35, H39, H42, W25, W31, W35, W45, S55, S58, E75, E76 and E85), manufactured by Dynamit Nobel.

Other pharmaceutically acceptable suppository bases may be substituted in whole or in part for the above-mentioned mono-, di- and triglycerides. The amount of base in the suppository is determined by the size (i.e. actual weight) of the dosage form, the amount of base (e.g., alginate) and drug used. Generally, the amount of suppository base is from about 20% to about 90% by weight of the total weight of the suppository. Preferably, the amount of suppository base in the suppository is from about 65% to about 80%, by weight of the total weight of the suppository.

Additional Embodiments

The oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones may be used as a substitute for the oxymorphone hydrochloride in any existing commercial product such as, e.g., Opana™, Opana ER™ and Numorphan™. Such formulations are listed in the FDA Orange Book.

EXAMPLES

The invention will now be illustrated by the following examples, showing the synthesis of the high purity oxymorphone, starting from oripavine.

FIG. **1** is the Powder X-Ray Diffraction pattern collected for a hydrated oxymorphone hydrochloride product made according to Example 3.2D.

Example 1.1A

Hydroxylation of Oripavine to 14-hydroxymorphinone

1 kg oripavine is added with stirring to a reaction vessel containing 2.76 kg of formic acid and 0.53 kg water, and stirring is continued until the oripavine is completely dissolved, and the temperature remains in the range 20-30° C. Subsequently, 0.36 kg of 35 wt % hydrogen peroxide solution

is added, and the reaction mixture is stirred for three hours or more, whilst maintaining the temperature in the range 20-35° C. The reaction vessel is cooled to 10° C. and 7.12 litres of dilute ammonium hydroxide is added slowly, whilst maintaining the reaction mixture below 40° C. If necessary, the pH of the reaction mixture is adjusted to the range 8 to 10, with more dilute ammonium hydroxide solution or hydrochloric acid as appropriate, and stirring is continued for 3-5 hours.

A precipitate of product 14-hydroxymorphinone is formed and filtered off. The precipitate is washed with water until colourless and then dried to a damp cake and collected for the next stage.

Example 1.1B

Formation of Oxymorphone Base

A hydrogenation vessel is charged with kg litre water and 0.73 kg acetic acid before adding 1 kg of 14-hydroxymorphinone prepared as in Example 1.1A and the mixture stirred until clear. 40 g of wet 10% Pd on carbon catalyst is added under a stream of nitrogen, and hydrogen supplied at 35-40 psi (2.41-2.76 bar). The temperature is maintained at 30±5° C. until hydrogen uptake stops, then the vessel is maintained at 35-40 psi (2.41-2.76 bar) and 30±5° C. for 3-4 hours. The reaction vessel is cooled to less than 25° C. and a sample subjected to HPLC to check for 14-hydroxymorphinone. If the 14-hydroxymorphinone area detected by HPLC is >0.1%, the hydrogenation is repeated.

Once it is assessed that the reaction is complete, the catalyst is filtered off, the pH of the filtrate is adjusted to pH 9 using ammonium hydroxide solution, the product precipitates and is isolated by filtration and dried under vacuum. The product is dissolved in dichloromethane/methanol (9:1 v/v) and slurried in florisil, filtered, and the filtrate is distilled to exchange to n-propanol. The n-propanol mixture is cooled and the product precipitates and is collected by filtration in 66% yield. A sample of product is tested by HPLC for alpha, beta unsaturated ketones, and is found to contain 0.51% by area measurement.

Example 1.1C

Formation of Highly Pure Oxymorphone Hydrochloride

A reaction vessel is charged with 1 kg of oxymorphone base, prepared as in Example 1.1B, together with 2.05 kg of absolute alcohol and 0.66 kg of water. The mixture is heated to 60±2° C. and stirred to form a slurry. A hydrochloric acid solution prepared from 0.66 kg concentrated hydrochloric acid, 0.24 kg of water and 0.31 kg of absolute alcohol is added to the oxymorphone base slurry and the pH checked to ensure that it is <1.0. 40 g of 10% Pd on carbon catalyst water-wet paste is added under a stream of nitrogen to the reaction mixture and the mixture is hydrogenated at 35±5 psi (2.41 bar) for 20 hours whilst maintaining a temperature of 65±3° C. The reaction mixture is filtered whilst hot through Celite and a 0.2 μm polish filter. The filtrate is cooled to 0-5° C. over 2-3 hours, and stirred for a further 2 hours to form oxymorphone hydrochloride as a precipitate. The precipitate is washed with absolute alcohol then dried. Yield is 80%.

A sample of the product is tested by HPLC for the presence of alpha, beta unsaturated ketones, and is found to contain 6.2 ppm.

Example 1.2A

Hydroxylation of Oripavine to 14-hydroxymorphinone

40 g of Oripavine is added with stirring to a reaction vessel containing 30 g of water and 85 g of formic acid, and stirring continued until oripavine is completely dissolved. The temperature remains in the range 20-30° C. Subsequently, 17.72 g of 30 wt % hydrogen peroxide solution is added, and the reaction mixture is stirred for three hours or more, whilst maintaining the temperature in the range 20-35° C. The reaction mixture is cooled to <20° C. and 335 mL of dilute ammonium hydroxide is added slowly, whilst maintaining the reaction mixture below 32° C. If necessary, the pH of the reaction mixture is adjusted to 9.0, with more dilute ammonium hydroxide solution or hydrochloric acid as appropriate, and stirring is continued for 2 hours at 20 C and 2 hours at 4-5° C.

A precipitate of 14-hydroxymorphinone is formed and filtered off. The precipitate is washed with water and then dried to a damp cake and collected for the next stage.

Example 1.2B

Formation of Oxymorphone Base

A hydrogenation vessel is charged with 148 g of water, 90.6 g of acetic acid, and 250 g of damp 14-hydroxymorphinone (48% water content), prepared as in Example 1.2A. The mixture is stirred until clear then 1.34 g of 10% Pd on carbon catalyst (dry weight) in the form of a paste is added under a stream of nitrogen. The hydrogenation vessel is flushed with nitrogen and hydrogen respectively, and then the reaction mixture is hydrogenated at 30° C. and 35 psi (2.41 bar) for 5 hours. An in process test by HPLC indicates an 14-hydroxymorphinone area of 0.07%.

Once it is assessed that the reaction is complete, the catalyst is filtered off through a pad of celite, and the celite cake is washed with 25 mL water. The filtrate is cooled to 0-5° C. and the pH is adjusted to 9.5±0.5 with 1:1 mixture (V/V) of concentrated ammonium hydroxide and water. The precipitate is stirred at 0-5° C. for one hour and isolated by filtration. The crude product is dried in vacuum oven at 50° C. to afford 113 g (86.9% yield) of light beige solid. A sample of product is tested by HPLC for alpha, beta unsaturated ketone, and is found to contain 0.27% by area measurement.

113 g of crude oxymorphone base is taken up in 1.13 L of dichloromethane/methanol (9:1, v/v). 113 g of florisil is added to the solution and the mixture is stirred for 12 hours. The mixture is filtered through a pad of 113 g of florisil, and the florisil cake is rinsed with 120 mL of dichloromethane/methanol. The solvent is removed by distillation and then switched to n-propanol. The batch is cooled to 0-5° C. and stirred for 1 hour to precipitate the oxymorphone base, which is filtered off, washed with cold n-propanol, and dried in a vacuum oven to afford 67.2 g (59.47%) of white solids.

A sample of product is tested by HPLC for alpha, beta unsaturated ketones, and is found to contain 0.027% by area measurement.

Example 1.2C

Formation of Highly Pure Oxymorphone Hydrochloride

A reaction vessel is charged with 50.1 g of oxymorphone base, prepared as in Example 1.2B, together with 120 g of absolute alcohol. The mixture is heated to 60±2° C. and stirred to form a slurry. A hydrochloric acid solution prepared from 32.7 g concentrated hydrochloric acid and 33.6 g of water is added to the oxymorphone base slurry and the pH is checked to ensure that it is <1.0. 2.0 g of 10% Pd on carbon catalyst water-wet paste is added under a stream of nitrogen to the reaction mixture and the mixture is hydrogenated at 35 psi (2.41 bar) for 20 hours whilst maintaining a temperature of 65° C. The reaction mixture is filtered whilst hot through Celite. The filtrate is cooled to 0-5° C. over 2-3 hours, and stirred for a further 2 hours to form oxymorphone hydrochloride as a precipitate. The precipitate is filtered off, washed with absolute alcohol and then dried to afford white crystals in 77% yield.

A sample of the product is tested by HPLC for the presence of alpha, beta unsaturated ketones, and is found to contain 1.1 ppm.

The above method may be varied by the skilled person whilst still maintaining excellent purity of the product oxymorphone hydrochloride, and examples of such variations follow.

Example 2.1B

Reduction of 14-hydroxymorphinone to Oxymorphone Base

A hydrogenation vessel is charged with 2.5 kg of water and 0.73 kg of acetic acid and 1 kg of 14-hydroxymorphinone is added to the vessel. The reaction mixture is stirred until a clear solution is obtained before 40 g of wet 10% Pd on carbon catalyst is added under a stream of nitrogen. Hydrogen is supplied at 35-40 psi (2.41-2.76 bar). The temperature is maintained at 30±5° C. until hydrogen uptake stops, then the vessel is maintained at 35-40 psi (2.41-2.76 bar) and 30±5° C. for 3-4 hours. The reaction vessel is cooled to less than 25° C. and a sample subjected to HPLC to check for 14-hydroxymorphinone. If the 14-hydroxymorphinone area detected by HPLC is >0.1%, the hydrogenation is repeated.

Once it is assessed that the reaction is complete, the catalyst is filtered off, dichloromethane/methanol (9:1 v/v) is added to the filtrate and the mixture is adjusted to pH 9-10 by adding ammonium hydroxide solution. The dichloromethane/methanol phase is separate, slurried in florisil, filtered, and the filtrate is distilled to exchange to n-propanol. The n-propanol mixture is cooled and the product precipitates and is collected by filtration in 73% yield. A sample of product is tested by HPLC for alpha, beta unsaturated ketones, and is found to contain 0.32% by area.

Example 2.2B

Reduction of 14-hydroxymorphinone to Oxymorphone Base

A hydrogenation vessel is charged with 35 g of water, 17 g of acetic acid and 38.08 g of 14-hydroxymorphinone, prepared in Example 1.2A. The reaction mixture is stirred until a clear solution is obtained before 1.8 g of wet 5% Pd on carbon catalyst is added under a stream of nitrogen. Hydrogen is supplied at 35-40 psi (2.41-2.76 bar). The temperature is maintained at 30±5° C. until hydrogen uptake stops, then the vessel is maintained at 35-40 psi (2.41-2.76 bar) and 30±5° C. for 4 hours. The reaction vessel is cooled to less than 25° C., and a sample is analyzed by HPLC to check for 14-hydroxymorphinone. The 14-hydroxymorphinone area detected by HPLC is 0.26%.

Once it is assessed that the reaction is complete, the catalyst is filtered off and the cake is washed with 15 mL of water. 180 mL of dichloromethane/methanol (9:1, v/v) are added to the filtrate and the pH of the mixture is adjusted to pH 9-10 by adding concentrated ammonium hydroxide. The dichloromethane/methanol layer is separated and purified by slurrying with ca. 20 g florisil. The slurry is filtered and the filtrate is distilled to exchange into n-propanol, and the mixture is cooled to 0-5° C. and stirred for 1-2 hours to precipitate oxymorphone base, which is isolated by filtration. The oxymorphone base is then slurried from n-propanol providing product in 74% yield. A sample of product is tested by HPLC for alpha, beta unsaturated ketones, and is found to contain 0.32% by area.

Example 2.2C

Formation of Highly Pure Oxymorphone Hydrochloride

A reaction vessel is charged with 2.5 g of oxymorphone base, prepared as in Example 2.2B, together with 7.5 mL of absolute alcohol, 2.5 g of water and 1.66 g of concentrated hydrochloric acid. The mixture is heated to 50-60° C. and a solution results. The pH is checked to ensure that it is <1.0. 0.111 g of 10% Pd on carbon catalyst water-wet paste is added under a stream of nitrogen to the reaction mixture and the mixture is hydrogenated at 35±5 psi (2.41 bar) for 21 hours whilst maintaining a temperature of 65±3° C. The reaction mixture is filtered whilst hot through a 0.45 μm filter. The filtrate is cooled to 0-5° C. over 2-3 hours, and stirred for a further 2 hours to form oxymorphone hydrochloride as a precipitate. The precipitate is filtered off, washed with cold absolute alcohol and dried under vacuum to afford white crystals in 77% yield.

A sample of the product is tested by HPLC for the presence of alpha, beta unsaturated ketones, and is found to contain 2.8 ppm.

Example 3.1B

Reduction of 14-hydroxymorphinone to Oxymorphone Hydrochloride

The procedure for forming the oxymorphinone free base is followed as shown above, but instead of isolating the free base from a dichloromethane/methanol solution, 0.35 volume equivalents of 3N hydrochloric acid are added (vs the volume of the dichloromethane/methanol solution), the reaction mixture is stirred, allowed to stand, and the aqueous layer (contains the product) is separated from the organic layer. The aqueous layer is distilled under vacuum to remove ca. 50% of the volume, and then the remaining solution is cooled over 2 hour to 20-25° C., stirred for 1-2 hours, cooled to 0-5° C. and stirred 2-3 hours. The white solids that form during stirring are filtered off and washed with cold isopropanol. The yield is 64% and the product contains 0.34% of alpha, beta unsaturated ketones.

Example 3.1C

Purification of Oxymorphone Hydrochloride

Using an analogous process to Example 1.1C, but starting from the product of Example 3.1B, purified oxymorphone hydrochloride is obtained in a yield of 92% and having an undetectable content of alpha, beta unsaturated ketones.

Example 3.2C

Preparation of Highly Pure Oxymorphone Hydrochloride

A reaction vessel is charged with 5.05 g of oxymorphone hydrochloride, prepared in Example 3.1B, together with 13.5 mL of absolute alcohol, 4.5 mL of water and 1.51 g of concentrated hydrochloric acid. The mixture is heated to 50-60° C. and a solution results. The pH is checked to ensure that it is <1.0. 0.21 g of 10% Pd on charcoal catalyst water-wet paste is added under a stream of nitrogen to the reaction mixture and the mixture is hydrogenated at 35±5 psi (2.41 bar) for 20 hours whilst maintaining a temperature of 65±3° C. The reaction mixture is filtered whilst hot through a 0.45 μm filter. The filtrate is cooled to 0-5° C. over 2-3 hours, and stirred for a further 2 hours to form a precipitate. The precipitate is collected by filtration, washed with cold absolute alcohol then dried. Yield is 92%.

A sample of the product is tested by HPLC and found to have an undetectable content of alpha, beta unsaturated ketones.

Without changing the basic process steps, but with small variations in the process steps for starting materials, such as isolation or not of such starting materials, and utilising the essential reduction requirements of the invention for the final step to the purified oxymorphone hydrochloride, other products have been obtained with levels of alpha, beta unsaturated ketones of 3.8 ppm, 1.7 ppm, 6.2 ppm, 6.9 ppm, 2.8 ppm, 3.1 ppm, 0.9 ppm, 6.0 ppm and another undetectable, or zero.

Example 3.2D

Hydration of Oxymorphone Hydrochloride

A drying dish is charged with oxymorphone hydrochloride, prepared as in Example 1.1C, 1.2C, 2.2C, 3.1C or 3.2C, which contains about 5-13 wt % of ethanol. The sample is placed in a vacuum oven along with a dish containing 100 mL of water. A vacuum is applied at 24-29 in Hg and the oven maintained at 20-40° C. for 24 hours. An ethanol-free or low ethanol (approx. 0.04 wt %) product is afforded containing about 10-13 wt % of water. The water absorbed by the sample may be removed in a vacuum oven at 50-55° C. The drying process is stopped when the product's KF is 6-8 wt %. The final hydrated oxymorphone hydrochloride affords a uniform polymorph with a consistent X-ray diffraction pattern.

What is claimed:

1. Oxymorphone hydrochloride having less than 10 ppm, as measured by HPLC, of 14-hydroxymorphinone.

2. Oxymorphone hydrochloride according to claim **1**, wherein the content of 14-hydroxymorphinone is less than 5 ppm.

3. A pharmaceutical formulation comprising at least one pharmaceutically acceptable excipient and the oxymorphone hydrochloride according to claim **1**.

4. A method of treating pain comprising administering a pharmaceutical formulation according to claim **3** to a patient in need thereof.

5. A method of purifying a starting material of either oxymorphone or oxymorphone hydrochloride to yield the oxymorphone hydrochloride according to claim **1**, comprising exposing the starting material oxymorphone or oxymorphone hydrochloride to hydrogen under reducing conditions in a strongly acid water and alcohol solvent reaction medium at a temperature in the range from 60 to 70° C. for a time sufficient to provide the less than 10 ppm of 14-hydroxymorphinone.

6. The method according to claim **5**, wherein the exposing is carried out for a period of at least 20 hours.

7. The method according to claim **5**, wherein the reaction medium has a pH of less than 1.

8. The method according to claim **5**, wherein the acid is hydrochloric acid.

9. The method according to claim **5**, wherein the temperature is approximately 65° C.

10. The method according to claim **5**, wherein the starting material oxymorphone or oxymorphone hydrochloride has not been isolated from a reaction mixture in which it is formed.

11. The method according to claim **5**, wherein the starting material oxymorphone or oxymorphone hydrochloride has been prepared by a process comprising reduction of 14-hydroxymorphinone.

12. The method according to claim **11**, wherein the 14-hydroxymorphinone that is reduced is prepared by a process of hydroxylating oripavine.

13. The method according to claim **12**, wherein the oripavine is derived from concentrated poppy straw.

14. The method according to claim **13**, wherein the concentrated poppy straw is derived from a high-Thebaine-yielding strain of poppy.

15. The method according to claim **5**, comprising the additional steps of subsequently forming crystalline oxymorphone hydrochloride and removing residual alcohol molecules from within the crystal structure of the crystalline oxymorphone hydrochloride by exposing the crystalline oxymorphone hydrochloride to water vapour, such that the residual alcohol molecules are displaced with water molecules.

16. The method according to claim **15**, comprising the additional step of removing some of the water molecules from within the crystal structure of the oxymorphone hydrochloride by exposure to reduced pressure.

17. The method according to claim **15**, comprising the additional step of removing some of the water molecules from within the crystal structure of the oxymorphone hydrochloride by heating the oxymorphone hydrochloride to a temperature in the range of from 50 to 55° C. under reduced pressure.

18. A method of making hydrated oxymorphone hydrochloride having less than 10 ppm, as measured by HPLC, of 14-hydroxymorphinone and a KF of 6-8 wt %, comprising exposing a starting material of oxymorphone or oxymorphone hydrochloride to gaseous hydrogen under reducing conditions in a strongly acid water and alcohol solvent reaction medium at a temperature in the range from 60 to 70° C., subsequently forming crystalline oxymorphone hydrochloride, and removing residual alcohol molecules from within the crystal structure of the crystalline oxymorphone hydrochloride by exposing the oxymorphone hydrochloride to water vapour, such that the residual alcohol molecules are displaced with water molecules.

19. Hydrated oxymorphone hydrochloride having less than 10 ppm, as measured by HPLC, of 14-hydroxymorphinone and having peaks within the following 20 ranges when analyzed by Powder X-Ray Diffraction: 8.5-9.5, 11.0-12.0, 11.5-12.5, 12.4-13.4, 15.2-16.2, 17.6-18.6, 19.3-20.3, 19.9-20.9, 24.6-25.6, 24.9-25.9, 29.0-30.0 and 31.0-32.0.

20. Oxymorphone hydrochloride prepared by the method of claim 5.

21. Hydrated oxymorphone hydrochloride prepared by the method of claim 18.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.	: 7,851,482 B2
APPLICATION NO.	: 11/866840
DATED	: December 14, 2010
INVENTOR(S)	: Jen-Sen Dung et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

At column 23, line 3, delete "20 ranges" and insert therefor --2Θ ranges--.

Signed and Sealed this
Nineteenth Day of July, 2011

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

US008309122B2

(12) **United States Patent**
Kao et al.

(10) **Patent No.: US 8,309,122 B2**
(45) **Date of Patent: *Nov. 13, 2012**

(54) **OXYMORPHONE CONTROLLED RELEASE FORMULATIONS**

(75) Inventors: **Huai-Hung Kao**, Syosset, NY (US); **Anand R. Baichwal**, Wappingers Falls, NY (US); **Troy McCall**, Smyma, GA (US); **David Lee**, Chadds Ford, PA (US)

(73) Assignee: **Endo Pharmaceuticals Inc.**, Chadds Ford, PA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1344 days.

This patent is subject to a terminal disclaimer.

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A61K 9/22 (2006.01)
A61K 9/34 (2006.01)
A61K 9/36 (2006.01)

(52) **U.S. Cl.** **424/464**; 424/468; 424/470; 424/479; 424/481; 424/482; 424/486

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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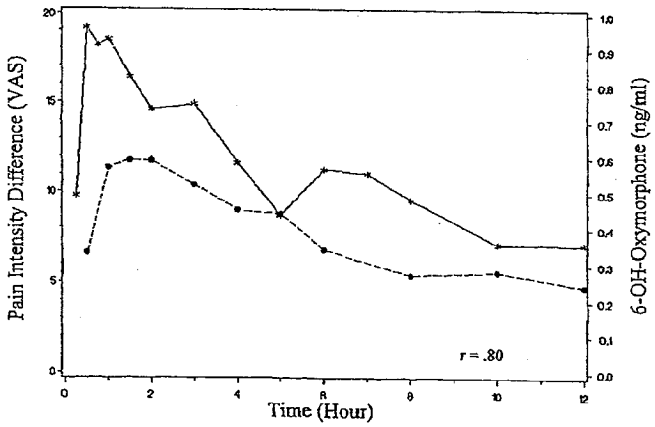
Primary Examiner — Lakshmi Channavajjala
(74) *Attorney, Agent, or Firm* — Mayer Brown LLP

(57) **ABSTRACT**

The invention pertains to a method of relieving pain by administering a controlled release pharmaceutical tablet containing oxymorphone which produces a mean minimum blood plasma level 12 to 24 hours after dosing, as well as the tablet producing the sustained pain relief.

20 Claims, 10 Drawing Sheets

PK Profile for 6-OH-Oxymorphone with PID Scores



* Pain Intensity Difference • 6-OH-Oxymorphone Plasma Concentrations

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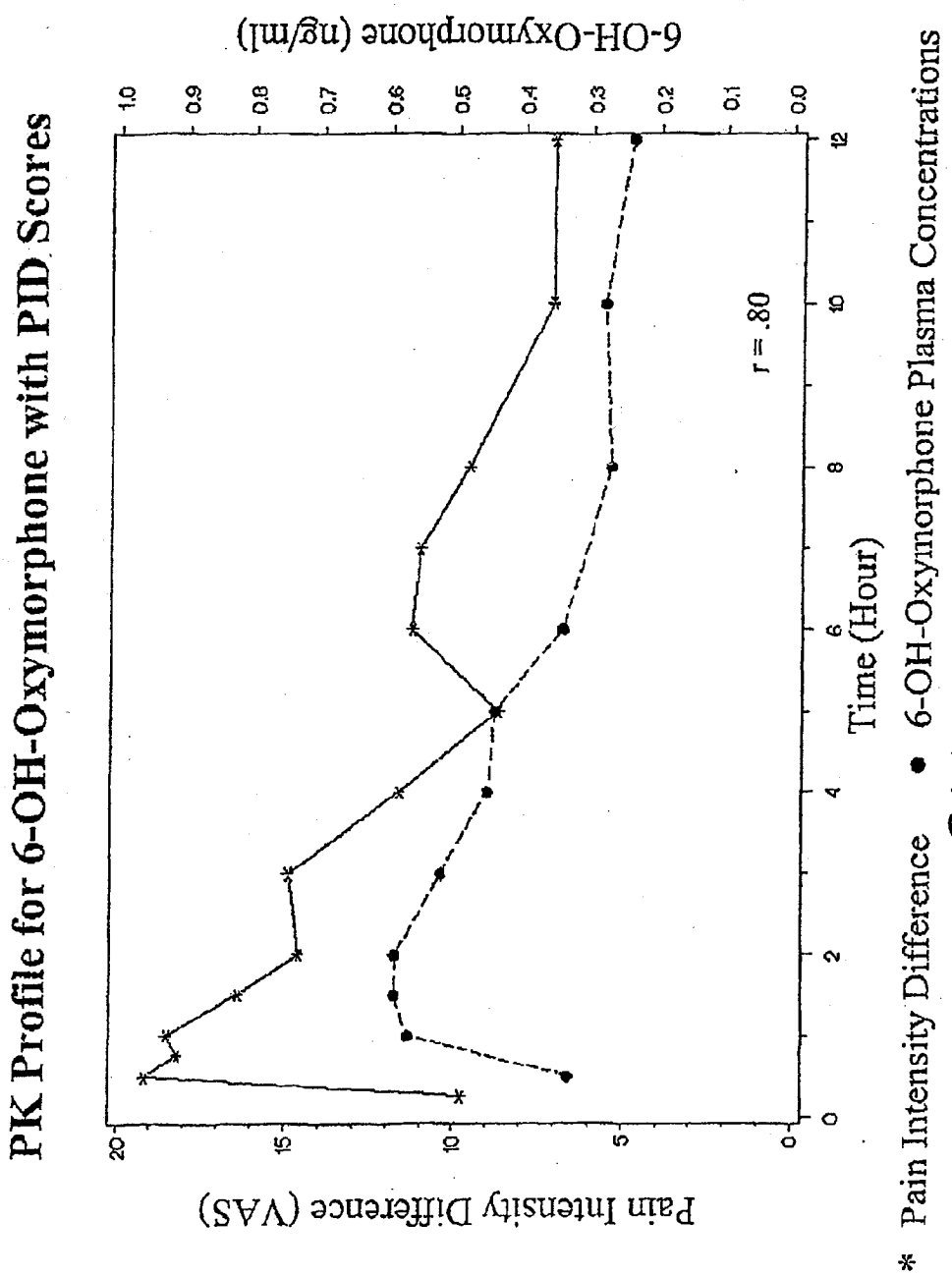
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6-OH-Oxymorphone (ng/ml)
Pain Intensity Difference (VAS)
Time (Hour)
r = .80
* Pain Intensity Difference • 6-OH-Oxymorphone Plasma Concentrations

FIG. 1

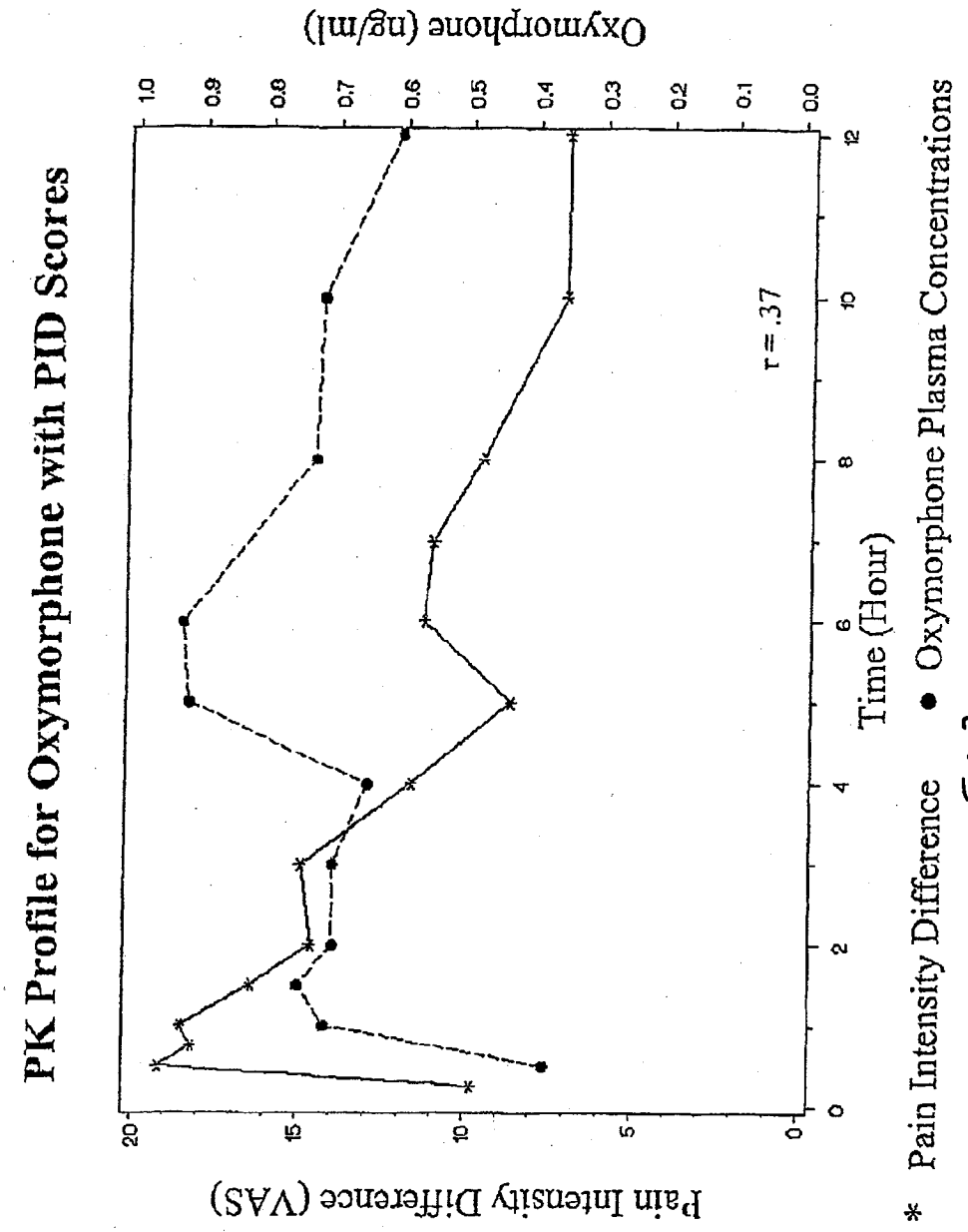
PK Profile for Oxymorphone with PID Scores
Pain Intensity Difference (VAS)
Oxymorphone (ng/ml)
Time (Hour)
r = .37
* Pain Intensity Difference • Oxymorphone Plasma Concentrations

FIG. 2

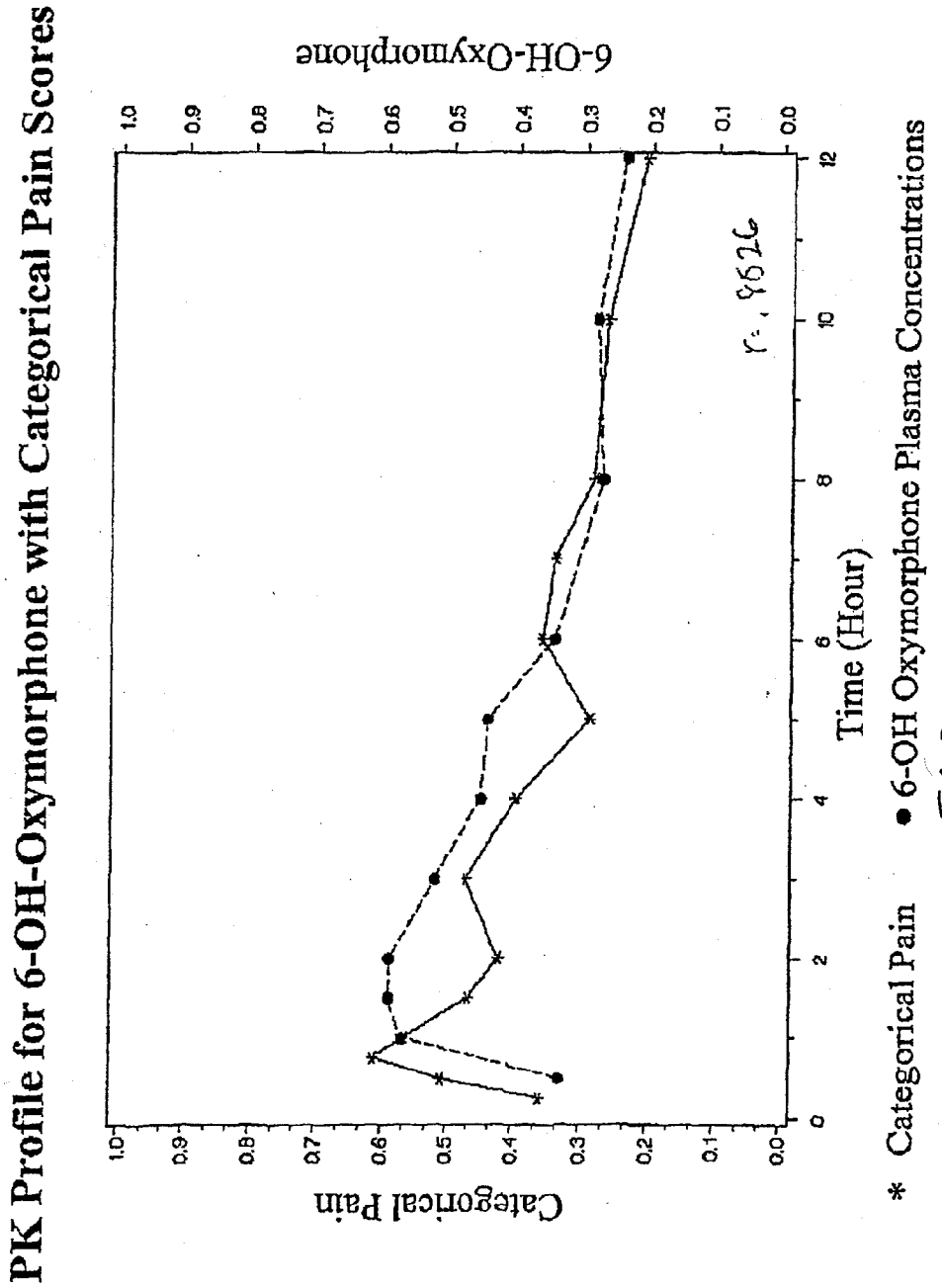
PK Profile for 6-OH-Oxymorphone with Categorical Pain Scores
6-OH-Oxymorphone
Categorical Pain
Time (Hour)
* Categorical Pain
• 6-OH Oxymorphone Plasma Concentrations
r-, 9626

Fig. 3

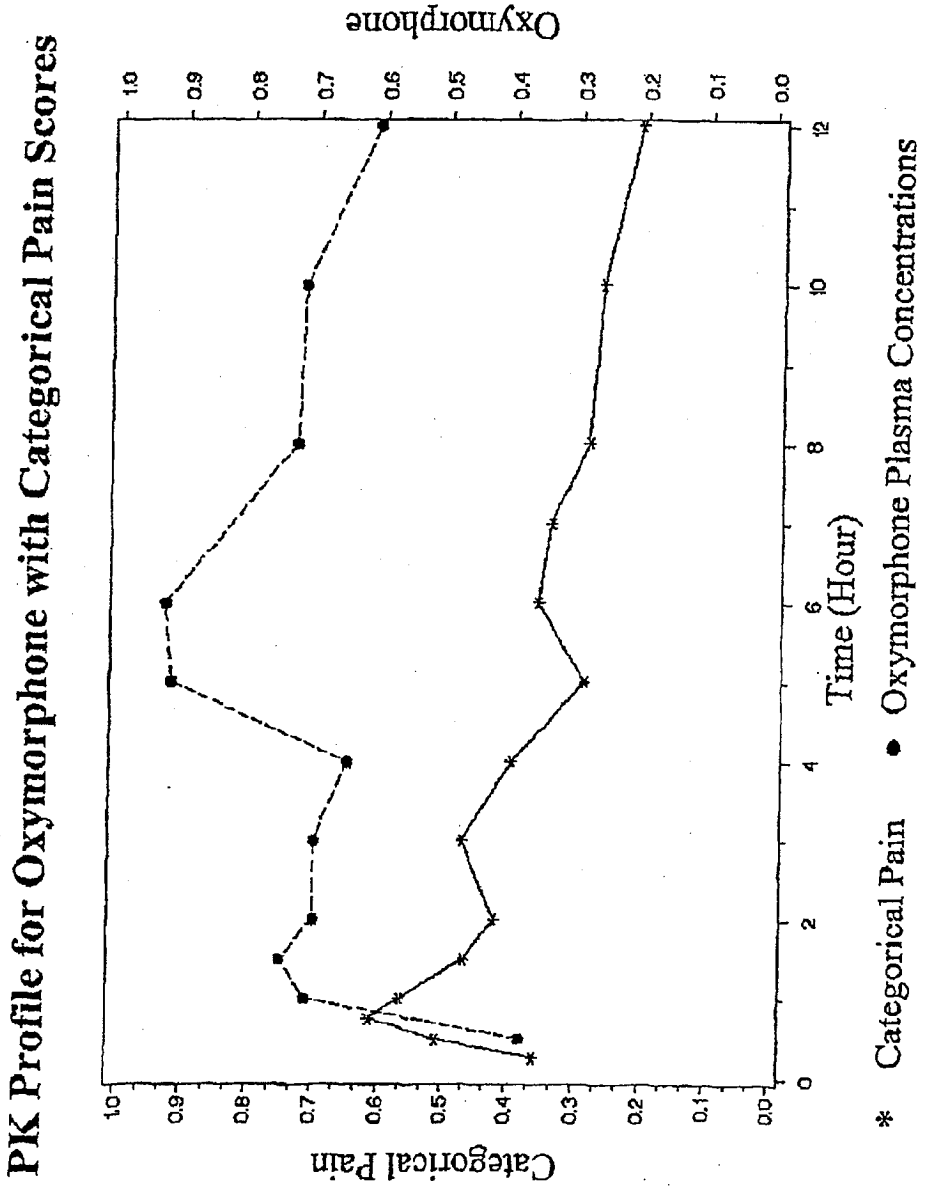
PK Profile for Oxymorphone with Categorical Pain Scores
Oxymorphone
Categorical Pain
Time (Hour)
* Categorical Pain
• Oxymorphone Plasma Concentrations

FIG. 4

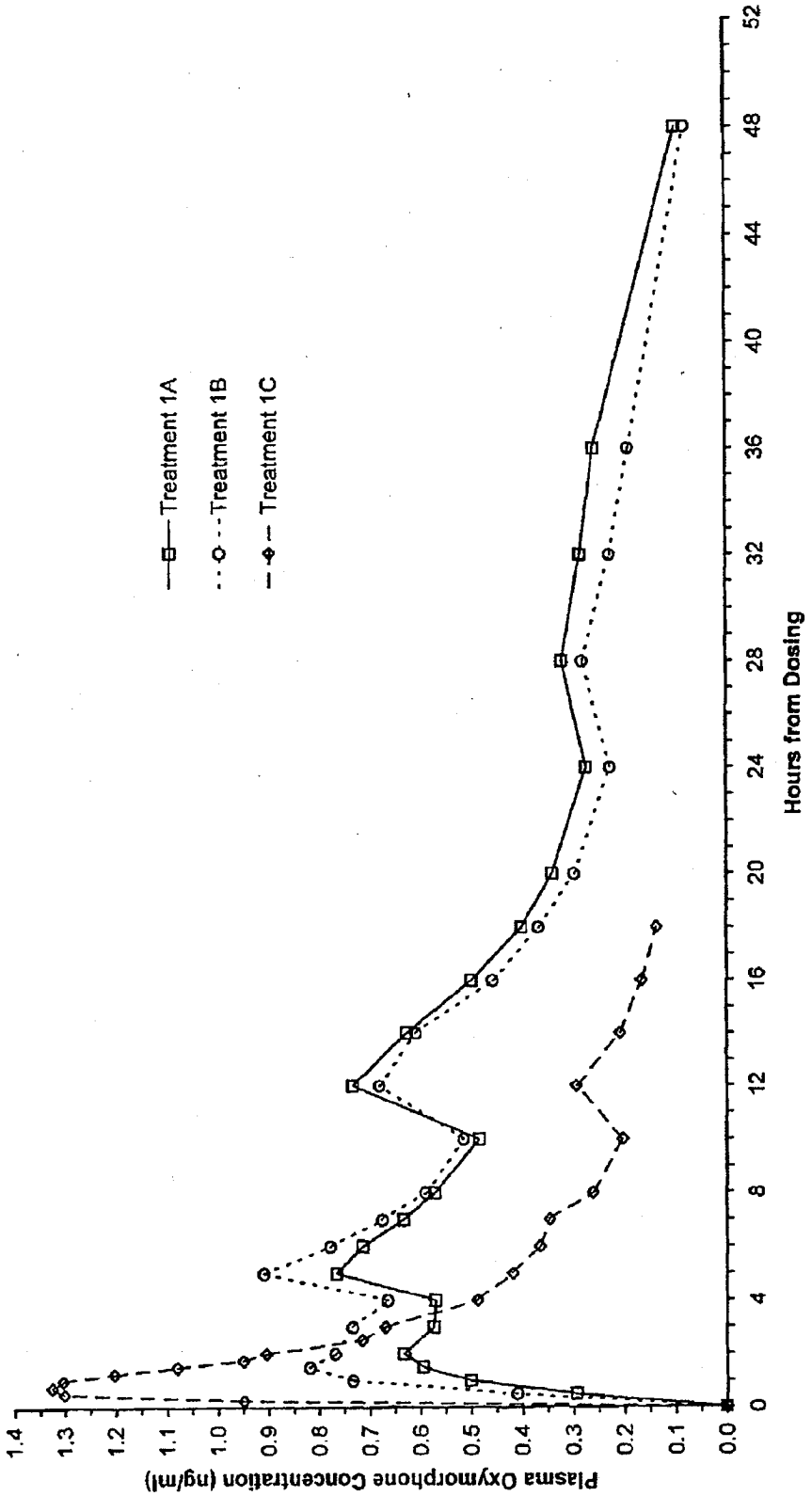
Treatment 1A
Treatment 1B
Treatment 1C
Plasma Oxymorphone Concentration (ng/ml)
Hours from Dosing
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
0
4
8
12
16
20
24
28
32
36
40
44
48
52

Figure 5

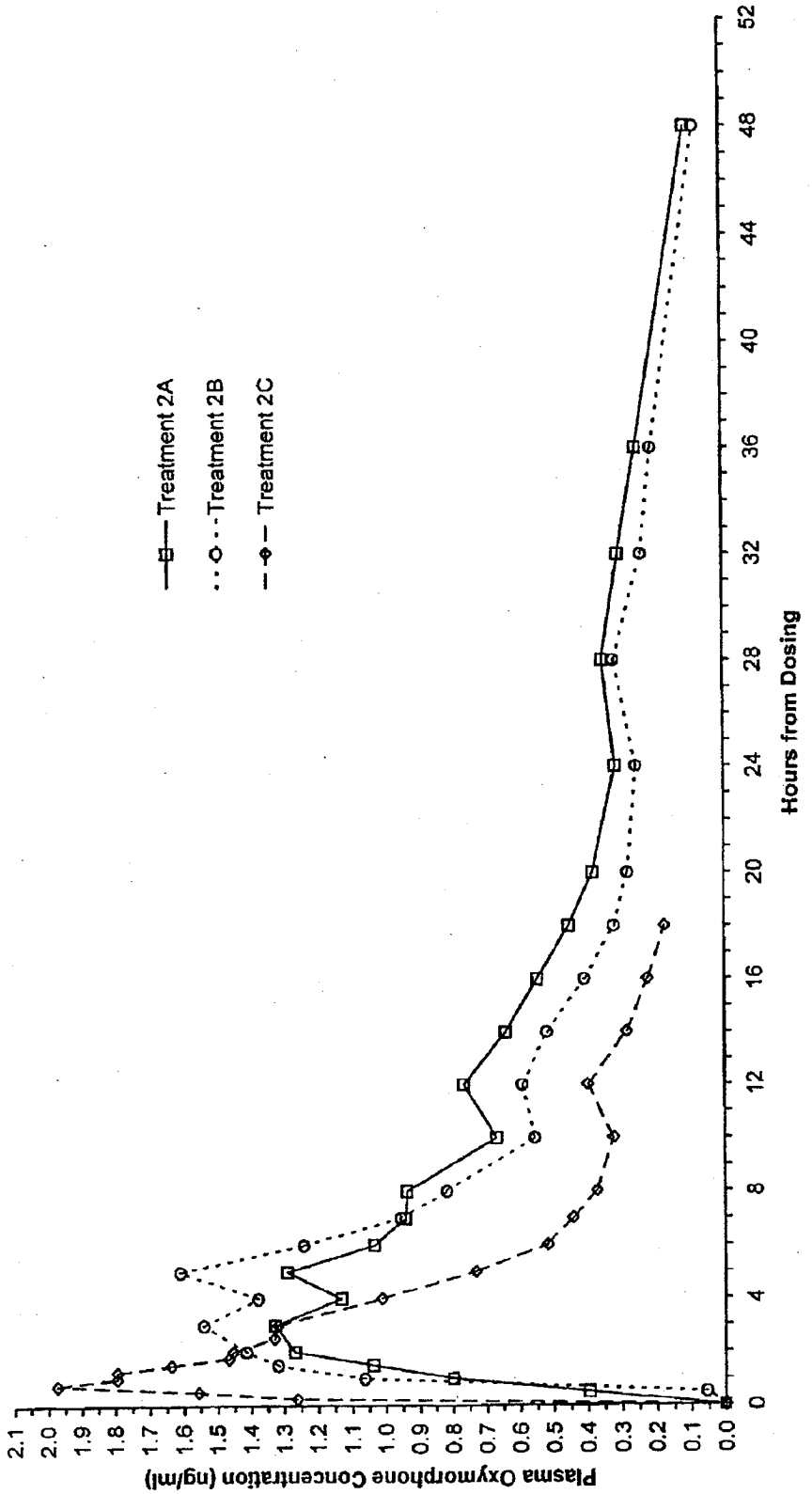
Treatment 2A
Treatment 2B
Treatment 2C
Plasma Oxymorphone Concentration (ng/ml)
Hours from Dosing
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
1.6
1.7
1.8
1.9
2.0
2.1
0
4
8
12
16
20
24
28
32
36
40
44
48
52

Figure 6

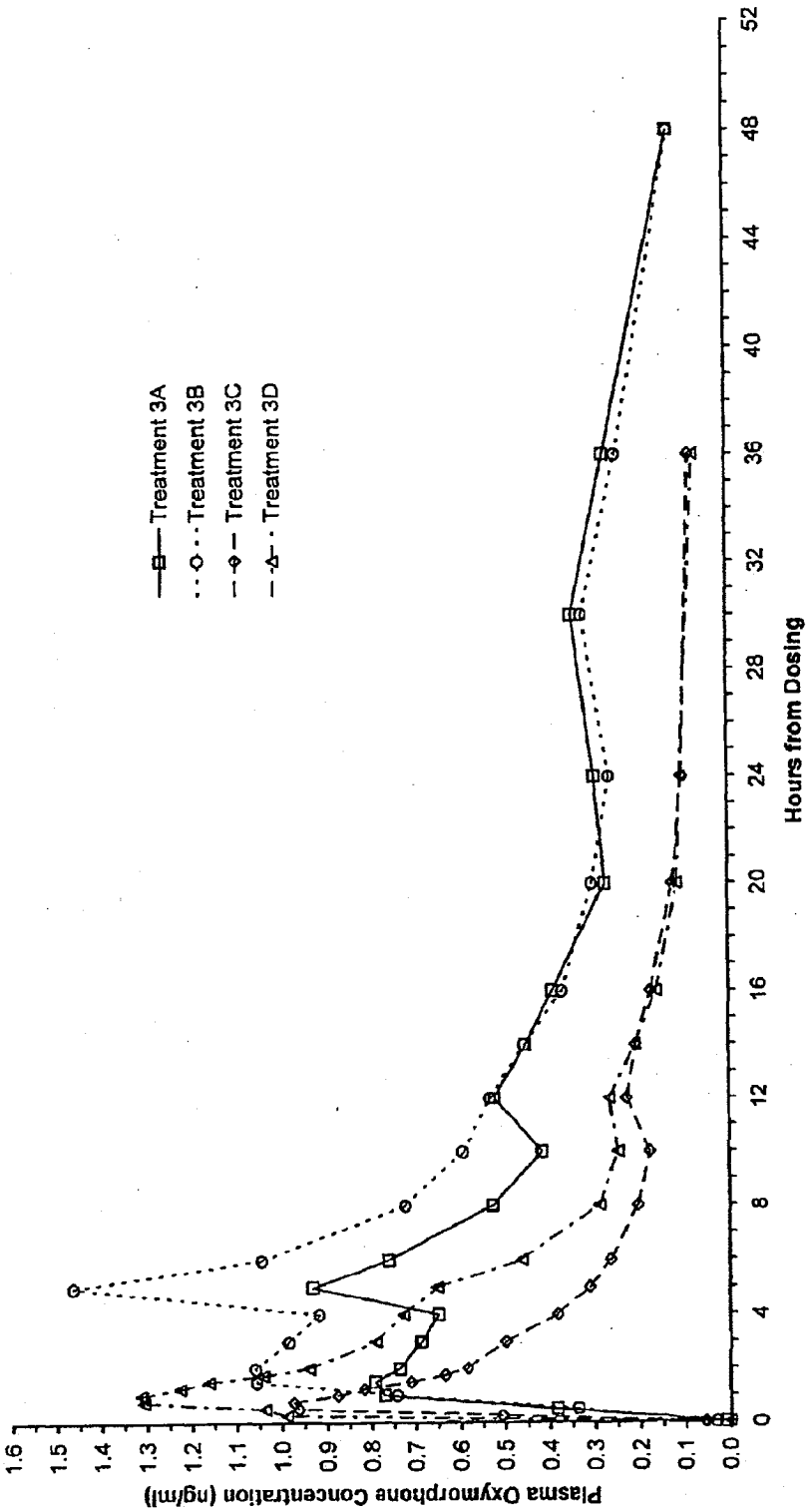
Treatment 3A
Treatment 3B
Treatment 3C
Treatment 3D
Plasma Oxymorphone Concentration (ng/ml)
Hours from Dosing
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
1.6
0
4
8
12
16
20
24
28
32
36
40
44
48
52

Figure 7

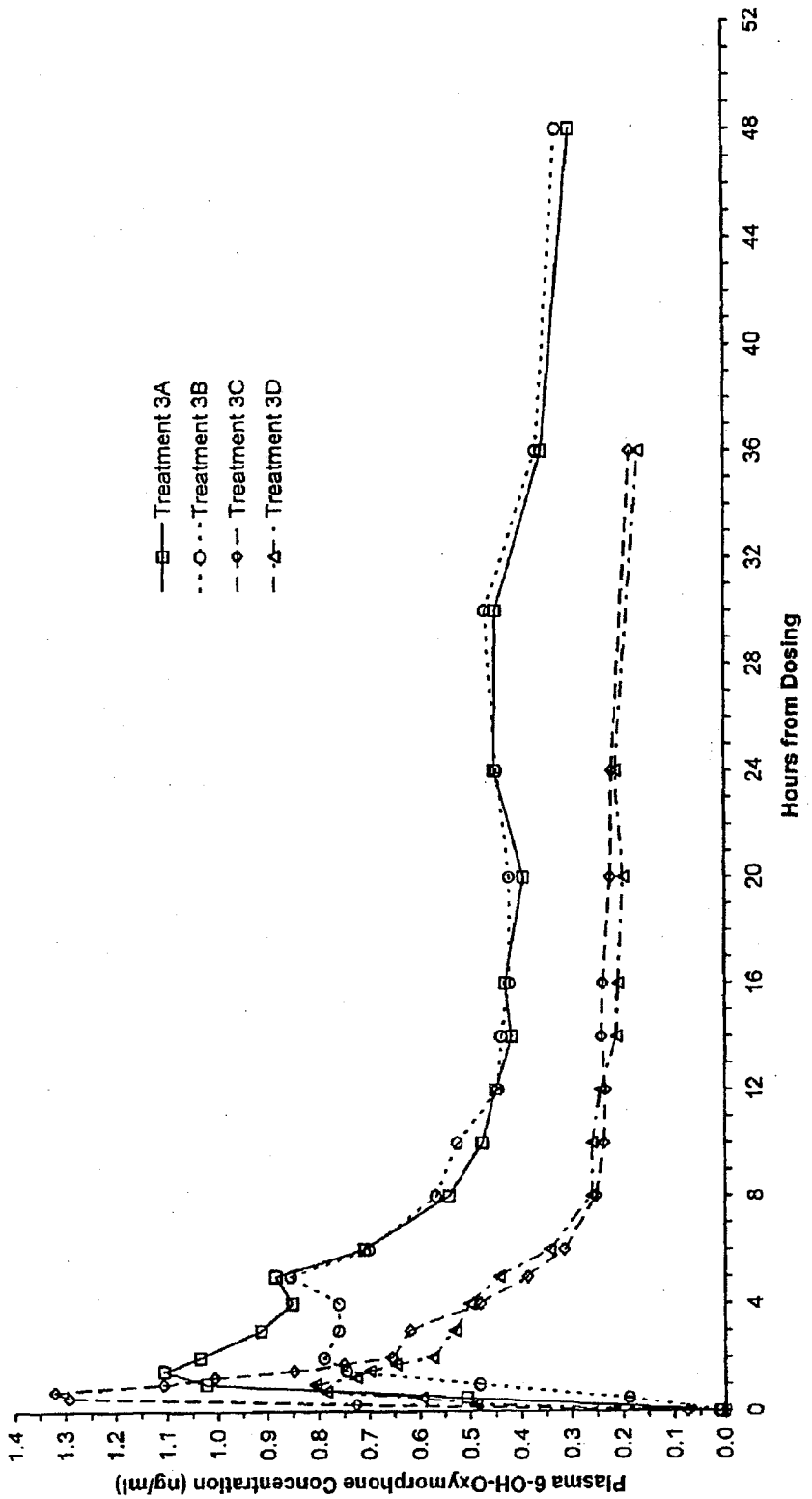
Treatment 3A
Treatment 3B
Treatment 3C
Treatment 3D
Plasma 6-OH-Oxymorphone Concentration (ng/ml)
Hours from Dosing
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
0
4
8
12
16
20
24
28
32
36
40
44
48
52

Figure 8

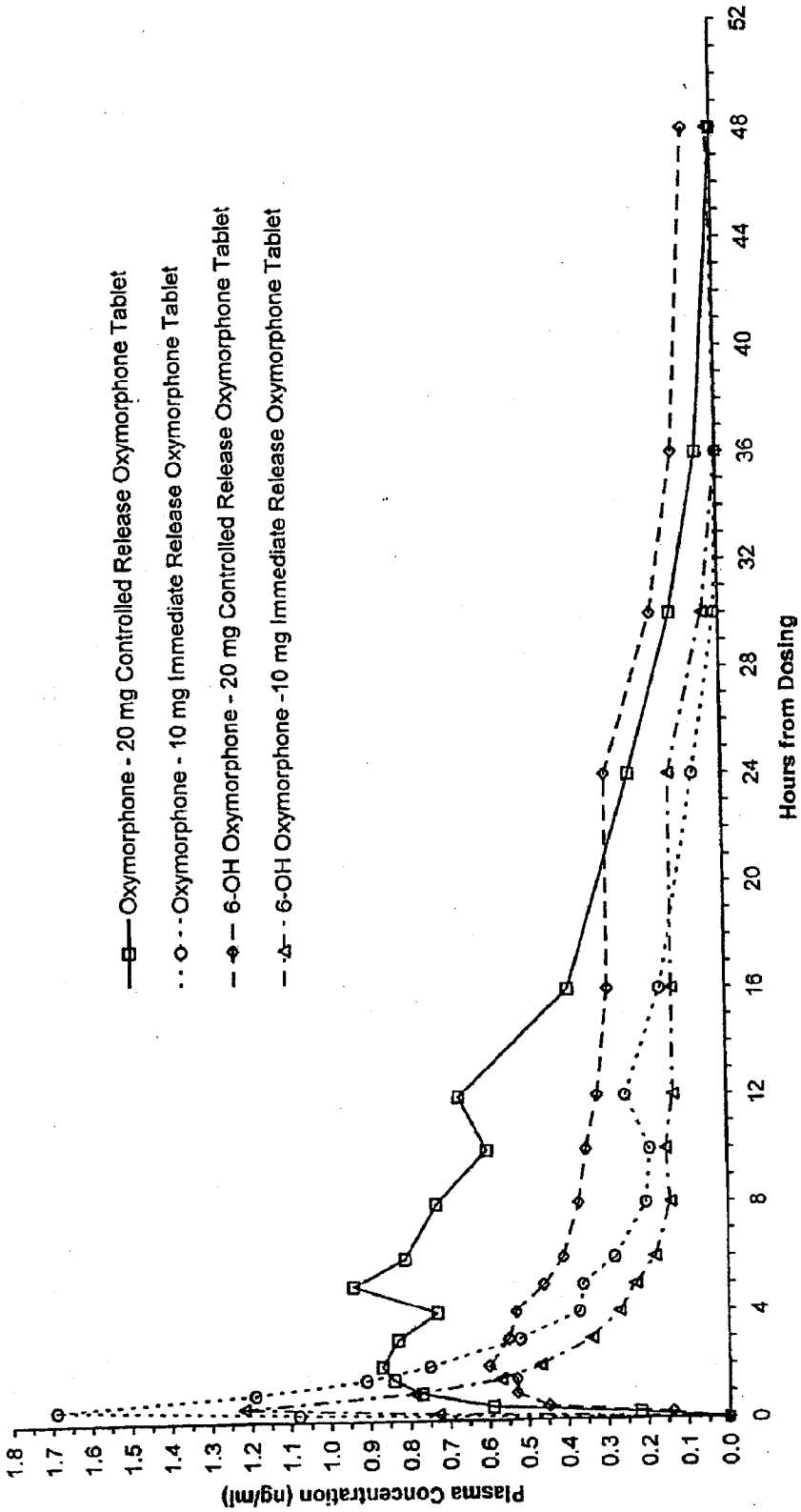
Oxymorphone - 20 mg Controlled Release Oxymorphone Tablet
Oxymorphone - 10 mg Immediate Release Oxymorphone Tablet
6-OH Oxymorphone - 20 mg Controlled Release Oxymorphone Tablet
6-OH Oxymorphone -10 mg Immediate Release Oxymorphone Tablet
Plasma Concentration (ng/ml)
Hours from Dosing
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
1.6
1.7
1.8
0
4
8
12
16
20
24
28
32
36
40
44
48
52

Figure 9

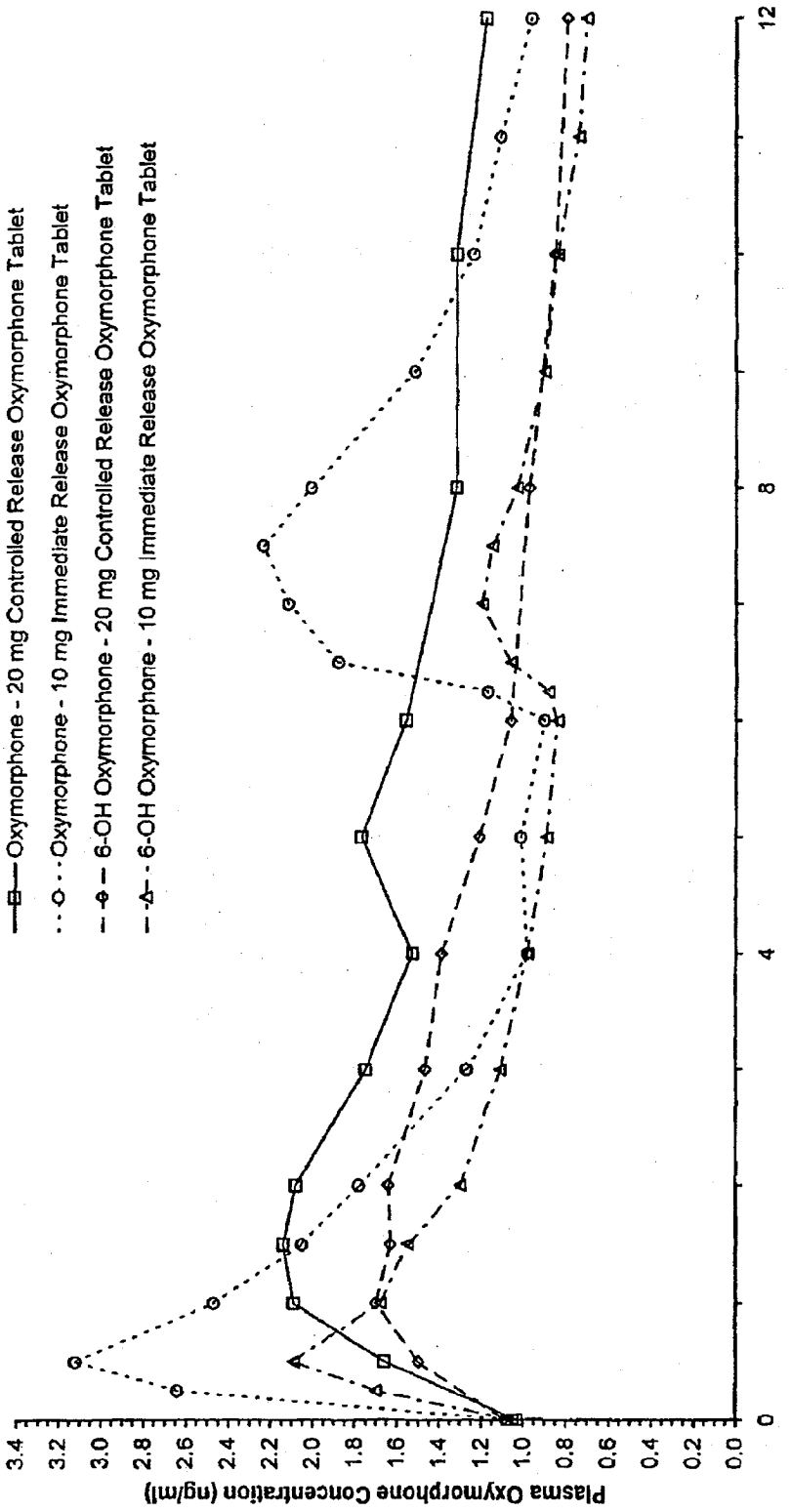
Oxymorphone - 20 mg Controlled Release Oxymorphone Tablet
Oxymorphone - 10 mg Immediate Release Oxymorphone Tablet
6-OH Oxymorphone - 20 mg Controlled Release Oxymorphone Tablet
6-OH Oxymorphone - 10 mg Immediate Release Oxymorphone Tablet
Plasma Oxymorphone Concentration (ng/ml)
Hours from Dosing
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
0
4
8
12

Figure 10

OXYMORPHONE CONTROLLED RELEASE FORMULATIONS

RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 10/190,192 filed Jul. 3, 2002 and claims priority to U.S. Provisional Patent Application Ser. Nos. 60/329,445 filed Oct. 15, 2001, 60/329,432 filed Oct. 15, 2001, 60/303,357 filed Jul. 6, 2001, and 60/329,444 filed Oct. 15, 2001, which are incorporated herein by reference to the extent permitted by law.

BACKGROUND OF THE INVENTION

Pain is the most frequently reported symptom and it is a common clinical problem which confronts the clinician. Many millions of people in the USA suffer from severe pain that, according to numerous recent reports, is chronically undertreated or inappropriately managed. The clinical usefulness of the analgesic properties of opioids has been recognized for centuries, and morphine and its derivatives have been widely employed for analgesia for decades in a variety of clinical pain states.

Oxymorphone HCl (14-hydroxydihydromorphinone hydrochloride) is a semi-synthetic phenanthrene-derivative opioid agonist, widely used in the treatment of acute and chronic pain, with analgesic efficacy comparable to other opioid analgesics. Oxymorphone is currently marketed as an injection (1 mg/ml in 1 ml ampules; 1.5 mg/ml in 1 ml ampules; 1.5 mg/ml in 10 ml multiple dose vials) for intramuscular, subcutaneous, and intravenous administration, and as 5 mg rectal suppositories. At one time, 2 mg, 5 mg and 10 mg oral immediate release (IR) tablet formulations of oxymorphone HCl were marketed. Oxymorphone HCl is metabolized principally in the liver and undergoes conjugation with glucuronic acid and reduction to 6-alpha- and beta-hydroxy epimers.

An important goal of analgesic therapy is to achieve continuous relief of chronic pain. Regular administration of an analgesic is generally required to ensure that the next dose is given before the effects of the previous dose have worn off. Compliance with opioids increases as the required dosing frequency decreases. Non-compliance results in suboptimal pain control and poor quality of life outcomes. (Ferrell B et al. Effects of controlled-release morphine on quality of life for cancer pain. *Oncol. Nur. Forum* 1989; 4:521-26). Scheduled, rather than "as needed" administration of opioids is currently recommended in guidelines for their use in chronic non-malignant pain. Unfortunately, evidence from prior clinical trials and clinical experience suggests that the short duration of action of immediate release oxymorphone would necessitate administration every 4-6 hours in order to maintain optimal levels of analgesia in chronic pain. A controlled release formulation which would allow less frequent dosing of oxymorphone would be useful in pain management.

For instance, a controlled release formulation of morphine has been demonstrated to provide patients fewer interruptions in sleep, reduced dependence on caregivers, improved compliance, enhanced quality of life outcomes, and increased control over the management of pain. In addition, the controlled release formulation of morphine was reported to provide more constant plasma concentration and clinical effects, less frequent peak to trough fluctuations, reduced dosing frequency, and possibly fewer side effects. (Thirlwell M P et al., Pharmacokinetics and clinical efficacy of oral morphine solution and controlled-release morphine tablets in cancer patients. *Cancer* 1989; 63:2275-83; Goughnour B R et al., Analgesic response to single and multiple doses of controlled-release morphine tablets and morphine oral solution in cancer patients. *Cancer* 1989; 63:2294-97; Ferrell B. et al., Effects of controlled-release morphine on quality of life for cancer pain. *Oncol. Nur. Forum* 1989; 4:521-26.

There are two factors associated with the metabolism of some drugs that may present problems for their use in controlled release systems. One is the ability of the drug to induce or inhibit enzyme synthesis, which may result in a fluctuating drug blood plasma level with chronic dosing. The other is a fluctuating drug blood level due to intestinal (or other tissue) metabolism or through a hepatic first-pass effect.

Oxymorphone is metabolized principally in the liver, resulting in an oral bioavailability of about 10%. Evidence from clinical experience suggests that the short duration of action of immediate release oxymorphone necessitates a four hour dosing schedule to maintain optimal levels of analgesia. It would be useful to clinicians and patients alike to have controlled release dosage forms of oxymorphone to use to treat pain and a method of treating pain using the dosage forms.

SUMMARY OF THE INVENTION

The present invention provides methods for relieving pain by administering a controlled release pharmaceutical tablet containing oxymorphone which produces at least a predetermined minimum blood plasma level for at least 12 hours after dosing, as well as tablets that produce the sustained pain relief over this time period.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a pharmacokinetic profile for 6-hydroxy oxymorphone with PID scores.

FIG. **2** is a pharmacokinetic profile for oxymorphone with PID scores.

FIG. **3** is a pharmacokinetic profile for 6-hydroxy oxymorphone with categorical pain scores.

FIG. **4** is a pharmacokinetic profile for oxymorphone with categorical pain scores.

FIG. **5** is a graph of the mean blood plasma concentration of oxymorphone versus time for clinical study 1.

FIG. **6** is a graph of the mean blood plasma concentration of oxymorphone versus time for clinical study 2.

FIG. **7** is a graph of the mean blood plasma concentration of oxymorphone versus time for clinical study 3.

FIG. **8** is a graph of the mean blood plasma concentration of 6-hydroxy oxymorphone versus time for clinical study 3.

FIG. **9** is a graph of the mean blood plasma concentration of oxymorphone for immediate and controlled release tablets from a single dose study.

FIG. **10** is a graph of the mean blood plasma concentration of oxymorphone for immediate and controlled release tablets from a steady state study.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides methods for alleviating pain for 12 to 24 hours using a single dose of a pharmaceutical composition by producing a blood plasma level of oxymorphone and/or 6-OH oxymorphone of at least a minimum value for at least 12 hours or more. As used herein, the terms "6-OH oxymorphone" and "6-hydroxy oxymorphone" are interchangeable and refer to the analog of oxymorphone hav-

ing an alcohol (hydroxy) moiety that replaces the carboxy moiety found on oxymorphone at the 6-position.

To overcome the difficulties associated with a 4-6 hourly dosing frequency of oxymorphone, this invention provides an oxymorphone controlled release oral solid dosage form, comprising a therapeutically effective amount of oxymorphone or a pharmaceutically acceptable salt of oxymorphone. It has been found that the decreased rate of release of oxymorphone from the oral controlled release formulation of this invention does not substantially decrease the bioavailability of the drug as compared to the same dose of a solution of oxymorphone administered orally. The bioavailability is sufficiently high and the release rate is such that a sufficient plasma level of oxymorphone and/or 6-OH oxymorphone is maintained to allow the controlled release dosage to be used to treat patients suffering moderate to severe pain with once or twice daily dosing. The dosing form of the present invention can also be used with thrice daily dosing.

It is critical when considering the present invention that the difference between a controlled release tablet and an immediate release formulation be fully understood. In classical terms, an immediate release formulation releases at least 80% of its active pharmaceutical ingredient within 30 minutes. With reference to the present invention, the definition of an immediate release formulation will be broadened further to include a formulation which releases more than about 80% of its active pharmaceutical ingredient within 60 minutes in a standard USP Paddle Method dissolution test at 50 rpm in 500 ml media having a pH of between 1.2 and 6.8 at 37° C. "Controlled release" formulations, as referred to herein, will then encompass any formulations which release no more than about 80% of their active pharmaceutical ingredients within 60 minutes under the same conditions.

The controlled release dosage form of this invention exhibits a dissolution rate in vitro, when measured by USP Paddle Method at 50 rpm in 500 ml media having a pH between 1.2 and 6.8 at 37° C., of about 15% to about 50% by weight oxymorphone released after 1 hour, about 45% to about 80% by weight oxymorphone released after 4 hours, and at least about 80% by weight oxymorphone released after 10 hours.

When administered orally to humans, an effective controlled release dosage form of oxymorphone should exhibit the following in vivo characteristics: (a) peak plasma level of oxymorphone occurs within about 1 to about 8 hours after administration; (b) peak plasma level of 6-OH oxymorphone occurs within about 1 to about 8 hours after administration; (c) duration of analgesic effect is through about 8 to about 24 hours after administration; (d) relative oxymorphone bioavailability is in the range of about 0.5 to about 1.5 compared to an orally-administered aqueous solution of oxymorphone; and (e) the ratio of the area under the curve of blood plasma level vs. time for 6-OH oxymorphone compared to oxymorphone is in the range of about 0.5 to about 1.5. Of course, there is variation of these parameters among subjects, depending on the size and weight of the individual subject, the subject's age, individual metabolism differences, and other factors. Indeed, the parameters may vary in an individual from day to day. Accordingly, the parameters set forth above are intended to be mean values from a sufficiently large study so as to minimize the effect of individual variation in arriving at the values. A convenient method for arriving at such values is by conducting a study in accordance with standard FDA procedures such as those employed in producing results for use in a new drug application (or abbreviated new drug application) before the FDA. Any reference to mean values herein, in conjunction with desired results, refer to results from such a study, or some comparable study. Reference to mean values reported herein for studies actually conducted are arrived at using standard statistical methods as would be employed by one skilled in the art of pharmaceutical formulation and testing for regulatory approval.

In one specific embodiment of the controlled release matrix form of the invention, the oxymorphone or salt of oxymorphone is dispersed in a controlled release delivery system that comprises a hydrophilic material which, upon exposure to gastrointestinal fluid, forms a gel matrix that releases oxymorphone at a controlled rate. The rate of release of oxymorphone from the matrix depends on the drug's partition coefficient between components of the matrix and the aqueous phase within the gastrointestinal tract. In a preferred form of this embodiment, the hydrophilic material of the controlled release delivery system comprises a mixture of a heteropolysaccharide gum and an agent capable of cross-linking the heteropolysaccharide in presence of gastrointestinal fluid. The controlled release delivery system may also comprise a water-soluble pharmaceutical diluent mixed with the hydrophilic material. Preferably, the cross-linking agent is a homopolysaccharide gum and the inert pharmaceutical diluent is a monosaccharide, a disaccharide, or a polyhydric alcohol, or a mixture thereof.

In a specific preferred embodiment, the appropriate blood plasma levels of oxymorphone and 6-hydroxy oxymorphone are achieved using oxymorphone in the form of oxymorphone hydrochloride, wherein the weight ratio of heteropolysaccharide to homopolysaccharide is in the range of about 1:3 to about 3:1, the weight ratio of heteropolysaccharide to diluent is in the range of about 1:8 to about 8:1, and the weight ratio of heteropolysaccharide to oxymorphone hydrochloride is in the range of about 10:1 to about 1:10. A preferred heteropolysaccharide is xanthan gum and a preferred homopolysaccharide is locust bean gum. The dosage form also comprises a cationic cross-linking agent and a hydrophobic polymer. In the preferred embodiment, the dosage form is a tablet containing about 5 mg to about 80 mg of oxymorphone hydrochloride. In a most preferred embodiment, the tablet contains about 20 mg oxymorphone hydrochloride.

The invention includes a method which comprises achieving appropriate blood plasma levels of drug while providing extended pain relief by administering one to three times per day to a patient suffering moderate to severe, acute or chronic pain, an oxymorphone controlled release oral solid dosage form of the invention in an amount sufficient to alleviate the pain for a period of about 8 hours to about 24 hours. This type and intensity of pain is often associated with cancer, autoimmune diseases, infections, surgical and accidental traumas and osteoarthritis.

The invention also includes a method of making an oxymorphone controlled release oral solid dosage form of the invention which comprises mixing particles of oxymorphone or a pharmaceutically acceptable salt of oxymorphone with granules comprising the controlled release delivery system, preferably followed by directly compressing the mixture to form tablets.

Pharmaceutically acceptable salts of oxymorphone which can be used in this invention include salts with the inorganic and organic acids which are commonly used to produce non-toxic salts of medicinal agents. Illustrative examples would be those salts formed by mixing oxymorphone with hydrochloric, sulfuric, nitric, phosphoric, phosphorous, hydrobromic, maleric, malic, ascorbic, citric or tartaric, pamoic, lauric, stearic, palmitic, oleic, myristic, lauryl sulfuric, naphthylenesulfonic, linoleic or linolenic acid, and the like. The hydrochloride salt is preferred.

It has now been found that 6-OH oxymorphone, which is one of the metabolites of oxymorphone, may play a role in alleviating pain. When oxymorphone is ingested, part of the dosage gets into the bloodstream to provide pain relief, while another part is metabolized to 6-OH oxymorphone. This metabolite then enters the bloodstream to provide further pain relief. Thus it is believed that both the oxymorphone and 6-hydroxyoxymorphone levels are important to pain relief.

The effectiveness of oxymorphone and 6-hydroxyoxymorphone at relieving pain and the pharmacokinetics of a single dose of oxymorphone were studied. The blood plasma levels of both oxymorphone and 6-hydroxyoxymorphone were measured in patients after a single dose of oxymorphone was administered. Similarly, the pain levels in patients were measured after a single administration of oxymorphone to determine the effective duration of pain relief from a single dose. FIGS. **1-2** show the results of these tests, comparing pain levels to oxymorphone and 6-hydroxy oxymorphone levels.

For these tests, pain was measured using a Visual Analog Scale (VAS) or a Categorical Scale. The VAS scales consisted of a horizontal line, 100 mm in length. The left-hand end of the scale (0 mm) was marked with the descriptor "No Pain" and the right-hand end of the scale (100 mm) was marked with the descriptor "Extreme Pain". Patients indicated their level of pain by making a vertical mark on the line. The VAS score was equal to the distance (in mm) from the left-hand end of the scale to the patient's mark. For the categorical scale, patients completed the following statement, "My pain at this time is" using the scale None=0, Mild=1, Moderate=2, or Severe=3.

As can be seen from these figures, there is a correlation between pain relief and both oxymorphone and 6-hydroxyoxymorphone levels. As the blood plasma levels of oxymorphone and 6-hydroxyoxymorphone increase, pain decreases (and pain intensity difference and pain relief increases). Thus, to the patient, it is the level of oxymorphone and 6-hydroxyoxymorphone in the blood plasma which is most important. Further it is these levels which dictate the efficacy of the dosage form. A dosage form which maintains a sufficiently high level of oxymorphone or 6-hydroxyoxymorphone for a longer period need not be administered frequently. Such a result is accomplished by embodiments of the present invention.

The oxymorphone controlled release oral solid dosage form of this invention can be made using any of several different techniques for producing controlled release oral solid dosage forms of opioid analgesics.

In one embodiment, a core comprising oxymorphone or oxymorphone salt is coated with a controlled release film which comprises a water insoluble material and which upon exposure to gastrointestinal fluid releases oxymorphone from the core at a controlled rate. In a second embodiment, the oxymorphone or oxymorphone salt is dispersed in a controlled release delivery system that comprises a hydrophilic material which upon exposure to gastrointestinal fluid forms a gel matrix that releases oxymorphone at a controlled rate. A third embodiment is a combination of the first two: a controlled release matrix coated with a controlled release film. In a fourth embodiment the oxymorphone is incorporated into an osmotic pump. In any of these embodiments, the dosage form can be a tablet, a plurality of granules in a capsule, or other suitable form, and can contain lubricants, colorants, diluents, and other conventional ingredients.

Osmotic Pump

An osmotic pump comprises a shell defining an interior compartment and having an outlet passing through the shell. The interior compartment contains the active pharmaceutical ingredient. Generally the active pharmaceutical ingredient is mixed with excipients or other compositions such as a polyalkylene. The shell is generally made, at least in part, from a material (such as cellulose acetate) permeable to the liquid of the environment where the pump will be used, usually stomach acid. Once ingested, the pump operates when liquid diffuses through the shell of the pump. The liquid dissolves the composition to produce a saturated situation. As more liquid diffuses into the pump, the saturated solution containing the pharmaceutical is expelled from the pump through the outlet. This produces a nearly constant release of active ingredient, in the present case, oxymorphone.

Controlled Release Coating

In this embodiment, a core comprising oxymorphone or oxymorphone salt is coated with a controlled release film which comprises a water insoluble material. The film can be applied by spraying an aqueous dispersion of the water insoluble material onto the core. Suitable water insoluble materials include alkyl celluloses, acrylic polymers, waxes (alone or in admixture with fatty alcohols), shellac and zein. The aqueous dispersions of alkyl celluloses and acrylic polymers preferably contain a plasticizer such as triethyl citrate, dibutyl phthalate, propylene glycol, and polyethylene glycol. The film coat can contain a water-soluble material such as polyvinylpyrrolidone (PVP) or hydroxypropylmethylcellulose (HPMC).

The core can be a granule made, for example, by wet granulation of mixed powders of oxymorphone or oxymorphone salt and a binding agent such as HPMC, or by coating an inert bead with oxymorphone or oxymorphone salt and a binding agent such as HPMC, or by spheronising mixed powders of oxymorphone or oxymorphone salt and a spheronising agent such as microcrystalline cellulose. The core can be a tablet made by compressing such granules or by compressing a powder comprising oxymorphone or oxymorphone salt.

The in vitro and in vivo release characteristics of this controlled release dosage form can be modified by using mixtures of different water insoluble and water soluble materials, using different plasticizers, varying the thickness of the controlled release film, including release-modifying agents in the coating, or by providing passageways through the coating.

Controlled Release Matrix

It is important in the present invention that appropriate blood plasma levels of oxymorphone and 6-hydroxy oxymorphone be achieved and maintained for sufficient time to provide pain relief to a patient for a period of 12 to 24 hours. The preferred composition for achieving and maintaining the proper blood plasma levels is a controlled-release matrix. In this embodiment, the oxymorphone or oxymorphone salt is dispersed in a controlled release delivery system that comprises a hydrophilic material (gelling agent) which upon exposure to gastrointestinal fluid forms a gel matrix that releases oxymorphone at a controlled rate. Such hydrophilic materials include gums, cellulose ethers, acrylic resins, and protein-derived materials. Suitable cellulose ethers include hydroxyalkyl celluloses and carboxyalkyl celluloses, especially hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), HPMC, and carboxy methylcellulose (CMC). Suitable acrylic resins include polymers and copolymers of acrylic acid, methacrylic acid, methyl acrylate and methyl methacrylate. Suitable gums include heteropolysaccharide and homopolysaccharide gums, e.g., xanthan, tragacanth, acacia, karaya, alginates, agar, guar, hydroxypropyl guar, carrageenan, and locust bean gums.

Preferably, the controlled release tablet of the present invention is formed from (I) a hydrophilic material comprising (a) a heteropolysaccharide; or (b) a heteropolysaccharide

and a cross-linking agent capable of cross-linking said heteropolysaccharide; or (c) a mixture of (a), (b) and a polysaccharide gum; and (II) an inert pharmaceutical filler comprising up to about 80% by weight of the tablet; and (III) oxymorphone.

The term "heteropolysaccharide" as used herein is defined as a water-soluble polysaccharide containing two or more kinds of sugar units, the heteropolysaccharide having a branched or helical configuration, and having excellent water-wicking properties and immense thickening properties.

A preferred heteropolysaccharide is xanthan gum, which is a high molecular weight (>10^6) heteropolysaccharide. Other preferred heteropolysaccharides include derivatives of xanthan gum, such as deacylated xanthan gum, the carboxymethyl ether, and the propylene glycol ester.

The cross linking agents used in the controlled release embodiment of the present invention which are capable of cross-linking with the heteropolysaccharide include homopolysaccharide gums such as the galactomannans, i.e., polysaccharides which are composed solely of mannose and galactose. Galactomannans which have higher proportions of unsubstituted mannose regions have been found to achieve more interaction with the heteropolysaccharide. Locust bean gum, which has a higher ratio of mannose to the galactose, is especially preferred as compared to other galactomannans such as guar and hydroxypropyl guar.

Preferably, the ratio of heteropolysaccharide to homopolysaccharide is in the range of about 1:9 to about 9:1, preferably about 1:3 to about 3:1. Most preferably, the ratio of xanthan gum to polysaccharide material (i.e., locust bean gum, etc.) is preferably about 1:1.

In addition to the hydrophilic material, the controlled release delivery system can also contain an inert pharmaceutical diluent such as a monosaccharide, a disaccharide, a polyhydric alcohol and mixtures thereof. The ratio of diluent to hydrophilic matrix-forming material is generally in the range of about 1:3 to about 3:1.

The controlled release properties of the controlled release embodiment of the present invention may be optimized when the ratio of heteropolysaccharide gum to homopolysaccharide material is about 1:1, although heteropolysaccharide gum in an amount of from about 20 to about 80% or more by weight of the heterodisperse polysaccharide material provides an acceptable slow release product. The combination of any homopolysaccharide gums known to produce a synergistic effect when exposed to aqueous solutions may be used in accordance with the present invention. It is also possible that the type of synergism which is present with regard to the gum combination of the present invention could also occur between two homogeneous or two heteropolysaccharides. Other acceptable gelling agents which may be used in the present invention include those gelling agents well-known in the art. Examples include vegetable gums such as alginates, carrageenan, pectin, guar gum, xanthan gum, modified starch, hydroxypropylmethylcellulose, methylcellulose, and other cellulosic materials such as sodium carboxymethylcellulose and hydroxypropyl cellulose. This list is not meant to be exclusive.

The combination of xanthan gum with locust bean gum with or without the other homopolysaccharide gums is an especially preferred gelling agent. The chemistry of certain of the ingredients comprising the excipients of the present invention such as xanthan gum is such that the excipients are considered to be self-buffering agents which are substantially insensitive to the solubility of the medicament and likewise insensitive to the pH changes along the length of the gastrointestinal tract.

The inert filler of the sustained release excipient preferably comprises a pharmaceutically acceptable saccharide, including a monosaccharide, a disaccharide, or a polyhydric alcohol, and/or mixtures of any of the foregoing. Examples of suitable inert pharmaceutical fillers include sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol, sorbitol, mixtures thereof and the like. However, it is preferred that a soluble pharmaceutical filler such as lactose, dextrose, sucrose, or mixtures thereof be used.

The cationic cross-linking agent which is optionally used in conjunction with the controlled release embodiment of the present invention may be monovalent or multivalent metal cations. The preferred salts are the inorganic salts, including various alkali metal and/or alkaline earth metal sulfates, chlorides, borates, bromides, citrates, acetates, lactates, etc. Specific examples of suitable cationic cross-linking agents include calcium sulfate, sodium chloride, potassium sulfate, sodium carbonate, lithium chloride, tripotassium phosphate, sodium borate, potassium bromide, potassium fluoride, sodium bicarbonate, calcium chloride, magnesium chloride, sodium citrate, sodium acetate, calcium lactate, magnesium sulfate and sodium fluoride. Multivalent metal cations may also be utilized. However, the preferred cationic cross-linking agents are bivalent. Particularly preferred salts are calcium sulfate and sodium chloride. The cationic cross-linking agents of the present invention are added in an amount effective to obtain a desirable increased gel strength due to the cross-linking of the gelling agent (e.g., the heteropolysaccharide and homopolysaccharide gums). In preferred embodiments, the cationic cross-linking agent is included in the sustained release excipient of the present invention in an amount from about 1 to about 20% by weight of the sustained release excipient, and in an amount about 0.5% to about 16% by weight of the final dosage form.

In the controlled release embodiments of the present invention, the sustained release excipient comprises from about 10 to about 99% by weight of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum, from about 1 to about 20% by weight of a cationic crosslinking agent, and from about 0 to about 89% by weight of an inert pharmaceutical diluent. In other embodiments, the sustained release excipient comprises from about 10 to about 75% gelling agent, from about 2 to about 15% cationic crosslinking agent, and from about 30 to about 75% inert diluent. In yet other embodiments, the sustained release excipient comprises from about 30 to about 75% gelling agent, from about 5 to about 10% cationic cross-linking agent, and from about 15 to about 65% inert diluent.

The sustained release excipient used in this embodiment of the present invention (with or without the optional cationic cross-linking agent) may be further modified by incorporation of a hydrophobic material which slows the hydration of the gums without disrupting the hydrophilic matrix. This is accomplished in preferred embodiments of the present invention by granulating the sustained release excipient with the solution or dispersion of a hydrophobic material prior to the incorporation of the medicament. The hydrophobic polymer may be selected from an alkylcellulose such as ethylcellulose, other hydrophobic cellulosic materials, polymers or copolymers derived from acrylic or methacrylic acid esters, copolymers of acrylic and methacrylic acid esters, zein, waxes, shellac, hydrogenated vegetable oils, and any other pharmaceutically acceptable hydrophobic material known to those skilled in the art. The amount of hydrophobic material incor-

porated into the sustained release excipient is that which is effective to slow the hydration of the gums without disrupting the hydrophilic matrix formed upon exposure to an environmental fluid. In certain preferred embodiments of the present invention, the hydrophobic material is included in the sustained release excipient in an amount from about 1 to about 20% by weight. The solvent for the hydrophobic material may be an aqueous or organic solvent, or mixtures thereof.

Examples of commercially available alkylcelluloses are Aquacoat coating (aqueous dispersion of ethylcellulose available from FMC of Philadelphia, Pa.) and Surelease coating (aqueous dispersion of ethylcellulose available from Colorcon of West Point, Pa.). Examples of commercially available acrylic polymers suitable for use as the hydrophobic material include Eudragit RS and RL polymers (copolymers of acrylic and methacrylic acid esters having a low content (e.g., 1:20 or 1:40) of quaternary ammonium compounds available from Rohm America of Piscataway, N.J.).

The controlled release matrix useful in the present invention may also contain a cationic cross-linking agent such as calcium sulfate in an amount sufficient to cross-link the gelling agent and increase the gel strength, and an inert hydrophobic material such as ethyl cellulose in an amount sufficient to slow the hydration of the hydrophilic material without disrupting it. Preferably, the controlled release delivery system is prepared as a pre-manufactured granulation.

EXAMPLES

Example 1

Two controlled release delivery systems are prepared by dry blending xanthan gum, locust bean gum, calcium sulfate dehydrate, and dextrose in a high speed mixed/granulator for 3 minutes. A slurry is prepared by mixing ethyl cellulose with alcohol. While running choppers/impellers, the slurry is added to the dry blended mixture, and granulated for another 3 minutes. The granulation is then dried to a LOD (loss on drying) of less than about 10% by weight. The granulation is then milled using 20 mesh screen. The relative quantities of the ingredients are listed in the table below.

TABLE 1

Controlled Release Delivery System

Excipient	Formulation 1 (%)	Formulation 2 (%)
Locust Bean Gum, FCC	25.0	30.0
Xanthan Gum, NF	25.0	30.0
Dextrose, USP	35.0	40.0
Calcium Sulfate Dihydrate, NF	10.0	0.0
Ethylcellulose, NF	5.0	0.0
Alcohol, SD3A (Anhydrous)	(10)[1]	(20.0)[1]
Total	100.0	100.0

A series of tablets containing different amounts of oxymorphone hydrochloride were prepared using the controlled release delivery Formulation 1 shown in Table 1. The quantities of ingredients per tablet are as listed in the following table.

TABLE 2

Sample Tablets of Differing Strengths

Component	Amounts in Tablet (mg)				
Oxymorphone HCl, USP (mg)	5	10	20	40	80
Controlled release delivery system	160	160	160	160	160
Silicified microcrystalline cellulose, N.F.	20	20	20	20	20
Sodium stearyl fumarate, NF	2	2	2	2	2
Total weight	187	192	202	222	262
Opadry (colored)	7.48	7.68	8.08	8.88	10.48
Opadry (clear)	0.94	0.96	1.01	1.11	1.31

Examples 2 and 3

Two batches of 20 mg tablets were prepared as described above, using the controlled release delivery system of Formulation 1. One batch was formulated to provide relatively fast controlled release, the other batch was formulated to provide relatively slow controlled release. Compositions of the tablets are shown in the following table.

TABLE 3

Slow and Fast Release Compositions

Ingredients	Example 2 Slow (mg)	Example 3 Fast (mg)	Example 4 Fast (mg)
Oxymorphone HCl, USP	20	20	20
Controlled Release Delivery System	360	160	160
Silicified Microcrystalline Cellulose, NF	20	20	20
Sodium stearyl fumarate, NF	4	2	2
Total weight	404	202	202
Coating (color or clear)	12	12	9

The tablets of Examples 2, 3, and 4 were tested for in vitro release rate according, to USP Procedure Drug Release U.S. Pat. No. 23. Release rate is a critical variable in attempting to control the blood plasma levels of oxymorphone and 6-hydroxyoxymorphone in a patient. Results are shown in the following Table 4.

TABLE 4

Release Rates of Slow and Fast Release Tablets

Time (hr)	Example 2 (Slow Release)	Example 3 (Fast Release)	Example 4 (Fast Release)
0.5	18.8	21.3	20.1
1	27.8	32.3	31.7
2	40.5	47.4	46.9
3	50.2	58.5	57.9
4	58.1	66.9	66.3
5	64.7	73.5	74.0
6	70.2	78.6	83.1
8	79.0	86.0	92.0
10	85.3	90.6	95.8
12	89.8	93.4	97.3

Clinical Studies

Three clinical studies were conducted to assess the bioavailability (rate and extent of absorption) of oxymorphone. Study 1 addressed the relative rates of absorption of con-

trolled release (CR) oxymorphone tablets (of Examples 2 and 3) and oral oxymorphone solution in fasted patients. Study 2 addressed the relative rates of absorption of CR oxymorphone tablets (of Examples 2 and 3) and oral oxymorphone solution in fed patients. Study 3 addressed the relative rates of absorption of CR oxymorphone tablets (of Example 4) and oral oxymorphone solution in fed and fasted patients.

The blood plasma levels set forth herein as appropriate to achieve the objects of the present invention are mean blood plasma levels. As an example, if the blood plasma level of oxymorphone in a patient 12 hours after administration of a tablet is said to be at least 0.5 ng/ml, any particular individual may have lower blood plasma levels after 12 hours. However, the mean minimum concentration should meet the limitation set forth. To determine mean parameters, a study should be performed with a minimum of 8 adult subjects, in a manner acceptable for filing an application for drug approval with the US Food and Drug Administration. In cases where large fluctuations are found among patients, further testing may be necessary to accurately determine mean values.

For all studies, the following procedures were followed, unless otherwise specified for a particular study.

The subjects were not to consume any alcohol-, caffeine-, or xanthine-containing foods or beverages for 24 hours prior to receiving study medication for each study period. Subjects were to be nicotine and tobacco free for at least 6 months prior to enrolling in the study. In addition, over-the-counter medications were prohibited 7 days prior to dosing and during the study. Prescription medications were not allowed 14 days prior to dosing and during the study.

Pharmacokinetic and Statistical Methods

The following pharmacokinetic parameters were computed from the plasma oxymorphone concentration-time data:

$AUC_{(0-t)}$	Area under the drug concentration-time curve from time zero to the time of the last quantifiable concentration (Ct), calculated using linear trapezoidal summation.
$AUC_{(0-inf)}$	Area under the drug concentration-time curve from time zero to infinity. $AUC_{(0-inf)} = AUC_{(0-t)} + Ct/K_{el}$, where K_{el} is the terminal elimination rate constant.
$AUC_{(0-24)}$	Partial area under the drug concentration-time curve from time zero to 24 hours.
C_{max}	Maximum observed drug concentration.
T_{max}	Time of the observed maximum drug concentration.
K_{el}	Elimination rate constant based on the linear regression of the terminal linear portion of the LN(concentration) time curve.

Terminal elimination rate constants for use in the above calculations were in turn computed using linear regression of a minimum of three time points, at least two of which were consecutive. K_{el} values for which correlation coefficients were less than or equal to 0.8 were not reported in the pharmacokinetic parameter tables or included in the statistical analysis. Thus $AUC_{(0-inf)}$ was also not reported in these cases.

A parametric (normal-theory) general linear model was applied to each of the above parameters (excluding T_{max}), and the LN-transformed parameters C_{max}, $AUC_{(0-24)}$, $AUC_{(0-t)}$, and $AUC_{(0-inf)}$. Initially, the analysis of variance (ANOVA) model included the following factors: treatment, sequence, subject within sequence, period, and carryover effect. If carryover effect was not significant, it was dropped from the model. The sequence effect was tested using the subject within sequence mean square, and all other main effects were tested using the residual error (error mean square).

Plasma oxymorphone concentrations were listed by subject at each collection time and summarized using descriptive statistics. Pharmacokinetic parameters were also listed by subject and summarized using descriptive statistics.

Study 1—Two Controlled Release Formulations; Fasted Patients

Healthy volunteers received a single oral dose of 20 mg CR oxymorphone taken with 240 ml water after a 10-hour fast. Subjects received the tablets of Example 2 (Treatment 1A) or Example 3 (Treatment 1B). Further subjects were given a single oral dose of 10 mg/10 ml oxymorphone solution in 180 ml apple juice followed with 60 ml water (Treatment 1C). The orally dosed solution was used to simulate an immediate release (IR) dose.

This study had a single-center, open-label, randomized, three-way crossover design using fifteen subjects. Subjects were in a fasted state following a 10-hour overnight fast. There was a 14-day washout interval between the three dose administrations. The subjects were confined to the clinic during each study period. Subjects receiving Treatment 1C were confined for 18 hours and subjects receiving Treatments 1A or 1B were confined for 48 hours after dosing. Ten-milliliter blood samples were collected during each study period at the 0 hour (predose), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, and 48 hours postdose for subjects receiving Treatment 1A or 1B and 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 18 hours post-dose. The mean plasma concentration of oxymorphone versus time for each treatment across all subjects is shown in table 5.

TABLE 5

Mean Plasma Concentration vs. Time (ng/ml)

Time (hr)	Treatment 1A	Treatment 1B	Treatment 1C
0	0.000	0.000	0.0000
0.25			0.9489
0.5	0.2941	0.4104	1.3016
0.75			1.3264
1	0.5016	0.7334	1.3046
1.25			1.2041
1.5	0.5951	0.8192	1.0813
1.75			0.9502
2	0.6328	0.7689	0.9055
2.5			0.7161
3	0.5743	0.7341	0.6689
4	0.5709	0.6647	0.4879
5	0.7656	0.9089	0.4184
6	0.7149	0.7782	0.3658
7	0.6334	0.6748	0.3464
8	0.5716	0.5890	0.2610
10	0.4834	0.5144	0.2028
12	0.7333	0.6801	0.2936
14	0.6271	0.6089	0.2083
16	0.4986	0.4567	0.1661
18	0.4008	0.3674	0.1368
20	0.3405	0.2970	
24	0.2736	0.2270	
28	0.3209	0.2805	
32	0.2846	0.2272	
36	0.2583	0.1903	
48	0.0975	0.0792	

The results are shown graphically in FIG. 5. In both Table 5 and FIG. 5, the results are normalized to a 20 mg dosage. The immediate release liquid of Treatment 1C shows a classical curve, with a high and relatively narrow peak, followed by an exponential drop in plasma concentration. However, the controlled release oxymorphone tablets exhibit triple peaks in blood plasma concentration. The first peak occurs (on average) at around 3 hours. The second peak of the mean blood plasma concentration is higher than the first, occurring around 6-7 hours, on average).

Occasionally, in an individual, the first peak is higher than the second, although generally this is not the case. This makes it difficult to determine the time to maximum blood plasma concentration (T_{max}) because if the first peak is higher than the second, maximum blood plasma concentration (C_{max}) occurs much earlier (at around 3 hours) than in the usual case where the second peak is highest. Therefore, when we refer to the time to peak plasma concentration (T_{max}) unless otherwise specified, we refer to the time to the second peak. Further, when reference is made to the second peak, we refer to the time or blood plasma concentration at the point where the blood plasma concentration begins to drop the second time. Generally, where the first peak is higher than the second, the difference in the maximum blood plasma concentration at the two peaks is small. Therefore, this difference (if any) was ignored and the reported C_{max} was the true maximum blood plasma concentration and not the concentration at the second peak.

TABLE 6

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 1

	Treatment 1A		Treatment 1B		Treatment 1C	
	Mean	SD	Mean	SD	Mean	SD
C_{max}	0.8956	0.2983	1.0362	0.3080	2.9622	1.0999
T_{max}	7.03	4.10	4.89	3.44	0.928	0.398
$AUC_{(0-t)}$	17.87	6.140	17.16	6.395	14.24	5.003
$AUC_{(0-inf)}$	19.87	6.382	18.96	6.908	16.99	5.830
$T_{1/2el}$	10.9	2.68	11.4	2.88	6.96	4.61

Units:
C_{max} in ng/ml,
T_{max} in hours,
AUC in ng * hr/ml,
$T_{1/2el}$ in hours.

Relative bioavailability determinations are set forth in Tables 7 and 8. For these calculations, AUC was normalized for all treatments to a 20 mg dose.

TABLE 7

Relative Bioavailability (F_{rel}) Determination Based on $AUC_{(0-inf)}$

F_{rel} (1A vs. 1C)	F_{rel} (1B vs. 1C)	F_{rel} (1A vs. 1B)
1.193 ± 0.203	1.121 ± 0.211	1.108 ± 0.152

TABLE 8

Relative Bioavailability Determination Based on $AUC_{(0-t)}$

F_{rel} (1A vs. 1C)	F_{rel} (1B vs. 1C)	F_{rel} (1A vs. 1B)
0.733 ± 0.098	0.783 ± 0.117	0.944 ± 0.110

Study 2—Two CR Formulations; Fed Patients

Healthy volunteers received a single oral dose of 20 mg CR oxymorphone taken with 240 ml water in a fed state. Subjects received the tablets of Example 2 (Treatment 2A) or Example 3 (Treatment 2B). Further subjects were given a single oral dose of 10 mg/10 ml oxymorphone solution in 180 ml apple juice followed with 60 ml water (Treatment 2C). The orally dosed solution was used to simulate an immediate release (IR) dose.

This study had a single-center, open-label, randomized, three-way crossover design using fifteen subjects. The subjects were in a fed state, after a 10-hour overnight fast followed by a standardized FDA high-fat breakfast. There was a 14-day washout interval between the three dose administrations. The subjects were confined to the clinic during each study period. Subjects receiving Treatment 2C were confined for 18 hours and subjects receiving Treatments 2A or 2B were confined for 48 hours after dosing. Ten-milliliter blood samples were collected during each study period at the 0 hour (predose), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, and 48 hours postdose for subjects receiving Treatment 2A or 2B and 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 18 hours postdose. The mean plasma concentration of oxymorphone versus time for each treatment across all subjects is shown in table 9.

TABLE 9

Mean Plasma Concentration vs. Time (ng/ml)

Time (hr)	Treatment 2A	Treatment 2B	Treatment 2C
0	0.000	0.000	0.0000
0.25			1.263
0.5	0.396	.0553	1.556
0.75			1.972
1	0.800	1.063	1.796
1.25			1.795
1.5	1.038	1.319	1.637
1.75			1.467
2	1.269	1.414	1.454
2.5			1.331
3	1.328	1.540	1.320
4	1.132	1.378	1.011
5	1.291	1.609	0.731
6	1.033	1.242	0.518
7	0.941	0.955	0.442
8	0.936	0.817	0.372
10	0.669	0.555	0.323
12	0.766	0.592	0.398
14	0.641	0.519	0.284
16	0.547	0.407	0.223
18	0.453	0.320	0.173
20	0.382	0.280	
24	0.315	0.254	
28	0.352	0.319	
32	0.304	0.237	
36	0.252	0.207	
48	0.104	0.077	

The results are shown graphically in FIG. 6. Again, the results have been normalized to a 20 mg dosage. As with Study 1, the immediate release liquid of Treatment 2C shows a classical curve, with a high and relatively narrow peak, followed by an exponential drop in plasma concentration, while the controlled release oxymorphone tablets exhibit triple peaks in blood plasma concentration. Thus, again when we refer to the time to peak plasma concentration (T_{max}) unless otherwise specified, we refer to the time to the second peak.

TABLE 10

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 2

	Treatment 2A		Treatment 2B		Treatment 2C	
	Mean	SD	Mean	SD	Mean	SD
C_{max}	1.644	0.365	1.944	0.465	4.134	0.897
T_{max}	3.07	1.58	2.93	1.64	0.947	0.313
$AUC_{(0-t)}$	22.89	5.486	21.34	5.528	21.93	5.044

TABLE 10-continued

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 2

	Treatment 2A		Treatment 2B		Treatment 2C	
	Mean	SD	Mean	SD	Mean	SD
$AUC_{(0\text{-}inf)}$	25.28	5.736	23.62	5.202	24.73	6.616
$T_{1/2el}$	12.8	3.87	11.0	3.51	5.01	2.02

Units:
C_{max} in ng/ml,
T_{max} in hours,
AUC in ng * hr/ml,
$T_{1/2el}$ in hours.

In Table 10, the T_{max} has a large standard deviation due to the two comparable peaks in blood plasma concentration. Relative bioavailability determinations are set forth in Tables 11 and 12.

TABLE 11

Relative Bioavailability Determination Based on $AUC_{(0\text{-}inf)}$

F_{rel} (2A vs. 2C)	F_{rel} (2B vs. 2C)	F_{rel} (2A vs. 2B)
1.052 ± 0.187	0.949 ± 0.154	1.148 ± 0.250

TABLE 12

Relative bioavailability Determination Based on $AUC_{(0\text{-}18)}$

F_{rel} (2A vs. 2C)	F_{rel} (2B vs. 2C)	F_{rel} (2A vs. 2B)
0.690 ± 0.105	0.694 ± 0.124	1.012 ± 0.175

As may be seen from tables 5 and 10 and FIGS. 1 and 2, the C_{max} for the CR tablets (treatments 1A, 1B, 2A and 2B) is considerably lower, and the T max much higher than for the immediate release oxymorphone. The blood plasma level of oxymorphone remains high well past the 8 (or even the 12) hour dosing interval desired for an effective controlled release tablet.

Study 3—One Controlled Release Formulation; Fed and Fasted Patients

This study had a single-center, open-label, analytically blinded, randomized, four-way crossover design. Subjects randomized to Treatment 3A and Treatment 3C, as described below, were in a fasted state following a 10-hour overnight fast. Subjects randomized to Treatment 3B and Treatment 3D, as described below, were in the fed state, having had a high fat meal, completed ten minutes prior to dosing. There was a 14-day washout interval between the four dose administrations. The subjects were confined to the clinic during each study period. Subjects assigned to receive Treatment 3A and Treatment 3B were discharged from the clinic on Day 3 following the 48-hour procedures, and subjects assigned to receive Treatment 3C and Treatment 3D were discharged from the clinic on Day 2 following the 36-hour procedures. On Day 1 of each study period the subjects received one of four treatments:

Treatments 3A and 3B: Oxymorphone controlled release 20 mg tablets from Example 3. Subjects randomized to Treatment 3A received a single oral dose of one 20 mg oxymorphone controlled release tablet taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 3B received a single oral dose of one 20 mg oxymorphone controlled release tablet taken with 240 ml of water 10 minutes after a standardized high fat meal.

Treatments 3C and 3D: oxymorphone HCl solution, USP, 1.5 mg/ml 10 ml vials. Subjects randomized to Treatment 3C received a single oral dose of 10 mg (6.7 ml) oxymorphone solution taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 3D received a single oral dose of 10 mg (6.7 ml) oxymorphone solution taken with 240 ml of water 10 minutes after a standardized high-fat meal.

A total of 28 male subjects were enrolled in the study, and 24 subjects completed the study. The mean age of the subjects was 27 years (range of 19 through 38 years), the mean height of the subjects was 69.6 inches (range of 64.0 through 75.0 inches), and the mean weight of the subjects was 169.0 pounds (range 117.0 through 202.0 pounds).

A total of 28 subjects received at least one treatment. Only subjects who completed all 4 treatments were included in the summary statistics and statistical analysis.

Blood samples (7 ml) were collected during each study period at the 0 hour (predose), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, 24, 30, 36, and 48 hours post-dose (19 samples) for subjects randomized to Treatment 3A and Treatment 3B. Blood samples (7 ml) were collected during each study period at the 0 hour (predose), and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, and 36 hours post-dose (21 samples) for subjects randomized to Treatment 3C and Treatment 3D.

The mean oxymorphone plasma concentration versus time curves for Treatments 3A, 3B, 3C, and 3D are presented in FIG. 7. The results have been normalized to a 20 mg dosage. The data is contained in Table 13. The arithmetic means of the plasma oxymorphone pharmacokinetic parameters and the statistics for all Treatments are summarized in Table 14.

TABLE 13

Mean Plasma Concentration vs. Time (ng/ml)

Time (hr)	Treatment 3A	Treatment 3B	Treatment 3C	Treatment 3D
0	0.0084	0.0309	0.0558	0.0000
0.25			0.5074	0.9905
0.5	0.3853	0.3380	0.9634	1.0392
0.75			0.9753	1.3089
1	0.7710	0.7428	0.8777	1.3150
1.25			0.8171	1.2274
1.5	0.7931	1.0558	0.7109	1.1638
1.75			0.6357	1.0428
2	0.7370	1.0591	0.5851	0.9424
3	0.6879	0.9858	0.4991	0.7924
4	0.6491	0.9171	0.3830	0.7277
5	0.9312	1.4633	0.3111	0.6512
6	0.7613	1.0441	0.2650	0.4625
8	0.5259	0.7228	0.2038	0.2895
10	0.4161	0.5934	0.1768	0.2470
12	0.5212	0.5320	0.2275	0.2660
14	0.4527	0.4562	0.2081	0.2093
16	0.3924	0.3712	0.1747	0.1623
20	0.2736	0.3021	0.1246	0.1144
24	0.2966	0.2636	0.1022	0.1065
30	0.3460	0.3231		
36	0.2728	0.2456	0.0841	0.0743
48	0.1263	0.1241		

TABLE 14

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 3

	Treatment 3B		Treatment 3A		Treatment 3C		Treatment 3D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max}	1.7895	0.6531	1.1410	0.4537	2.2635	1.0008	3.2733	1.3169
T_{max}	5.56	9.39	5.57	7.14	0.978	1.14	1.11	0.768
$AUC_{(0-24)}$	14.27	4.976	11.64	3.869	12.39	4.116	17.30	5.259
$AUC_{(0-t)}$	19.89	6.408	17.71	8.471	14.53	4.909	19.20	6.030
$AUC_{(0-inf)}$	21.29	6.559	19.29	5.028	18.70	6.618	25.86	10.03
$T_{1/2el}$	12.0	3.64	12.3	3.99	16.2	11.4	20.6	19.3

The relative bioavailability calculations are summarized in tables 15 and 16.

TABLE 15

Relative Bioavailability Determination Based on $AUC_{(0-inf)}$

F_{rel} (3A vs. 3C)	F_{rel} (3B vs. 3D)	F_{rel} (3D vs. 3C)	F_{rel} (3B vs. 3A)
1.040 ± 0.1874	0.8863 ± 0.2569	1.368 ± 0.4328	1.169 ± 0.2041

TABLE 16

Relative Bioavailability Determination Based on $AUC_{(0-24)}$

F_{rel} (3A vs. 3C)	F_{rel} (3B vs. 3D)	F_{rel} (3D vs. 3C)	F_{rel} (3B vs. 3A)
0.9598 ± 0.2151	0.8344 ± 0.100	1.470 ± 0.3922	1.299 ± 0.4638

The objectives of this study were to assess the relative bioavailability of oxymorphone from oxymorphone controlled release (20 mg) compared to oxymorphone oral solution (10 mg) under both fasted and fed conditions, and to determine the effect of food on the bioavailability of oxymorphone from the controlled release formulation, oxymorphone CR, and from the oral solution.

The presence of a high fat meal had a substantial effect on the oxymorphone C_{max}, but less of an effect on oxymorphone AUC from oxymorphone controlled release tablets. Least Squares (LS) mean C_{max} was 58% higher and LS mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were 18% higher for the fed condition (Treatment B) compared to the fasted condition (Treatment A) based on LN-transformed data. This was consistent with the relative bioavailability determination from $AUC_{(0-inf)}$ since mean F_{rel} was 1.17. Mean T_{max} values were similar (approximately 5.6 hours), and no significant difference in T_{max} was shown using nonparametric analysis. Half value durations were significantly different between the two treatments.

The effect of food on oxymorphone bioavailability from the oral solution was more pronounced, particularly in terms of AUC. LS mean C_{max} was 50% higher and LS mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were 32-34% higher for the fed condition (Treatment D) compared to the fasted condition (Treatment C) based on LN-transformed data. This was consistent with the relative bioavailability determination from $AUC_{(0-inf)}$ since mean F_{rel} was 1.37. Mean T_{max}(approximately 1 hour) was similar for the two treatments and no significant difference was shown.

Under fasted conditions, oxymorphone controlled release 20 mg tablets exhibited similar extent of oxymorphone availability compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment A versus Treatment C). From LN-transformed data, LS mean $AUC_{(0-t)}$ was 17% higher for oxymorphone CR, whereas LS mean $AUC_{(0-inf)}$ values were nearly equal (mean ratio=99%). Mean F_{rel} values calculated from $AUC_{(0-inf)}$ and $AUC_{(0-24)}$, (1.0 and 0.96, respectively) also showed similar extent of oxymorphone availability between the two treatments.

As expected, there were differences in parameters reflecting rate of absorption. LS mean C_{max} was 49% lower for oxymorphone controlled release tablets compared to the dose-normalized oral solution, based on LN-transformed data. Half-value duration was significantly longer for the controlled release formulation (means, 12 hours versus 2.5 hours).

Under fed conditions, oxymorphone availability from oxymorphone controlled release 20 mg was similar compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment B versus Treatment D). From LN-transformed data, LS mean $AUC_{(0-inf)}$ was 12% lower for oxymorphone CR. Mean F_{rel} values calculated from $AUC_{(0-inf)}$ and $AUC_{(0-24)}$, (0.89 and 0.83 respectively) also showed similar extent of oxymorphone availability from the tablet. As expected, there were differences in parameters reflecting rate of absorption. LS mean C_{max} was 46% lower for oxymorphone controlled release tablets compared to the dose-normalized oral solution, based on LN-transformed data. Mean T_{max} was 5.7 hours for the tablet compared to 1.1 hours for the oral solution. Half-value duration was significantly longer for the controlled release formulation (means, 7.8 hours versus 3.1 hours).

The presence of a high fat meal did not appear to substantially affect the availability of 6-hydroxyoxymorphone following administration of oxymorphone controlled release tablets. LS mean ratios were 97% for $AUC_{(0-t)}$ and 91% for C_{max} (Treatment B versus A), based on LN-transformed data. This was consistent with the relative bioavailability determination from $AUC_{(0-24)}$, since mean F_{rel} was 0.97. Mean T_{max} was later for the fed treatment compared to the fasted treatment (5.2 and 3.6 hours, respectively), and difference was significant.

Under the fasted conditions, oxymorphone controlled release 20 mg tablets exhibited similar availability of 6-hydroxyoxymorphone compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment A versus Treatment C). From LN-transformed data, LS mean ration for $AUC_{(0-t)}$ was 104.5%. Mean F_{rel} (0.83) calculated from $AUC_{(0-24)}$ also showed similar extent of oxymorphone availability between the two treatments. Mean T_{max} was 3.6 hours for the tablet compared to 0.88 for the oral solution. Half-values duration was significantly longer for the controlled release formulation (means, 11 hours versus 2.2 hours).

Under fed conditions, availability of 6-hydroxyoxymorphone from oxymorphone controlled release 20 mg was similar compared to 10 mg oxymorphone oral solution normal-

ized to a 20 mg dose (Treatment B versus Treatment D). From LN-transformed data, LS mean $AUC_{(0-t)}$ was 14% higher for oxymorphone CR. Mean F_{rel} (0.87) calculated from $AUC_{(0-24)}$ also indicted similar extent of availability between the treatments. Mean T_{max} was 5.2 hours for the tablet compared to 1.3 hour for the oral solution. Half-value duration was significantly longer for the controlled release formulation (means, 14 hours versus 3.9 hours).

The extent of oxymorphone availability from oxymorphone controlled release 20 mg tablets was similar under fed and fasted conditions since there was less than a 20% difference in LS mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ values for each treatment, based on LN-transformed data. T_{max} was unaffected by food; however, LS mean C_{max} was increased 58% in the presence of the high fat meal. Both rate and extent of oxymorphone absorption from the oxymorphone oral solution were affected by food since LS mean C_{max} and AUC values were increased approximately 50 and 30%, respectively. T_{max} was unaffected by food. Under both fed and fasted conditions, oxymorphone controlled release tablets exhibited similar extent of oxymorphone availability compared to oxymorphone oral solution since there was less than a 20% difference in LS mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ values for each treatment.

Bioavailability of 6-hydroxyoxymorphone following oxymorphone controlled release 20 mg tablets was also similar under fed and fasted conditions since there was less than a 20% difference in LS mean C_{max} and AUC values for each treatment. T_{max} was later for the fed condition. The presence of food did not affect the extent of availability from oxymorphone oral solution since LS mean AUC values were less than 20% different. However, C_{max} was decreased 35% in the presence of food. T_{max}, was unaffected by food. Under both fed and fasted conditions, oxymorphone controlled release tablets exhibited similar extent availability compared to oxymorphone oral solution since there was less than a 20% difference in LS mean AUC values for each treatment.

The mean 6-OH oxymorphone plasma concentration versus time curves for Treatments 3A, 3B, 3C, and 3D are presented in FIG. **8**. The data is contained in Table 17.

TABLE 17

Mean Plasma Concentration vs. Time (ng/ml)
6-Hydroxyoxymorphone

Time (hr)	Treatment 3A	Treatment 3B	Treatment 3C	Treatment 3D
0	0.0069	0.0125	0.0741	0.0000
0.25			0.7258	0.4918
0.5	0.5080	0.1879	1.2933	0.5972
0.75			1.3217	0.7877

TABLE 17-continued

Mean Plasma Concentration vs. Time (ng/ml)
6-Hydroxyoxymorphone

Time (hr)	Treatment 3A	Treatment 3B	Treatment 3C	Treatment 3D
1	1.0233	0.4830	1.1072	0.8080
1.25			1.0069	0.7266
1.5	1.1062	0.7456	0.8494	0.7001
1.75			0.7511	0.6472
2	1.0351	0.7898	0.6554	0.5758
3	0.9143	0.7619	0.6196	0.5319
4	0.8522	0.7607	0.4822	0.5013
5	0.8848	0.8548	0.3875	0.4448
6	0.7101	0.7006	0.3160	0.3451
8	0.5421	0.5681	0.2525	0.2616
10	0.4770	0.5262	0.2361	0.2600
12	0.4509	0.4454	0.2329	0.2431
14	0.4190	0.4399	0.2411	0.2113
16	0.4321	0.4230	0.2385	0.2086
20	0.3956	0.4240	0.2234	0.1984
24	0.4526	0.4482	0.2210	0.2135
30	0.4499	0.4708		
36	0.3587	0.3697	0.1834	0.1672
48	0.3023	0.3279		

TABLE 18

Pharmacokinetic Parameters of Plasma 6-Hydroxymorphone for Study 3

	Treatment 3A		Treatment 3B		Treatment 3C		Treatment 3D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max}	1.2687	0.5792	1.1559	0.4848	1.5139	0.7616	0.9748	0.5160
T_{max}	3.61	7.17	5.20	9.52	0.880	0.738	1.30	1.04
$AUC_{(o-t)}$	22.47	10.16	22.01	10.77	10.52	4.117	9.550	4.281
$AUC_{(o-inf)}$	38.39	23.02	42.37	31.57	20.50	7.988	23.84	11.37
$T_{1/2el}$	39.1	36.9	39.8	32.6	29.3	12.0	44.0	35.00

Study 4—Controlled Release 20 mg vs. Immediate Release 10 mg

A study was conducted to compare the bioavailability and pharmacokinetics of controlled release and immediate release oxymorphone tablets under single-dose and multiple-dose (steady state) conditions. For the controlled release study, healthy volunteers received a single dose of a 20 mg controlled release oxymorphone table on the morning of Day 1. Beginning on the morning of Day 3, the volunteers were administered a 20 mg controlled release oxymorphone tablet every 12 hours through the morning dose of Day 9. For the immediate release study, healthy volunteers received a single 10 mg dose of an immediate release oxymorphone tablet on the morning of Day 1. On the morning of Day 3, additional 10 mg immediate release tablets were administered every six hours through the first two doses on Day 9.

FIG. **9** shows the average plasma concentrations of oxymorphone and 6-hydroxyoxymorphone for all subjects after a single dose either controlled release (CR) 20 mg or immediate release (IR) 10 mg oxymorphone. The data in the figure (as with the other relative experimental data herein) is normalized to a 20 mg dose. The immediate release tablet shows a classical curve, with a high, relatively narrow peak followed

by an exponential drop in plasma concentration. The controlled release oxymorphone tablets show a lower peak with extended moderate levels of oxymorphone and 6-hydroxy oxymorphone. Table 19 shows the levels of oxymorphone and 6-hydroxy oxymorphone from FIG. 9 in tabular form.

TABLE 19

Mean Plasma Concentration (ng/ml)

	Oxymorphone		6-Hydroxyoxymorphone	
Hour	Controlled Release 20 mg	Immediate Release 10 mg	Controlled Release 20 mg	Immediate Release 10 mg
0.00	0.00	0.00	0.00	0.00
0.25	0.22	1.08	0.14	0.73
0.50	0.59	1.69	0.45	1.22
1.00	0.77	1.19	0.53	0.79
1.50	0.84	0.91	0.53	0.57
2.00	0.87	0.75	0.60	0.47
3.00	0.83	0.52	0.55	0.34
4.00	0.73	0.37	0.53	0.27
5.00	0.94	0.36	0.46	0.23
6.00	0.81	0.28	0.41	0.18
8.00	0.73	0.20	0.37	0.14
10.0	0.60	0.19	0.35	0.15
12.0	0.67	0.25	0.32	0.13
16.0	0.39	0.16	0.29	0.13
24.0	0.23	0.07	0.29	0.13
30.0	0.12	0.01	0.17	0.04
36.0	0.05	0.00	0.11	0.00
48.0	0.00	0.00	0.07	0.01

FIG. 10 shows the average plasma concentrations of oxymorphone and 6-hydroxyoxymorphone for all subjects in the steady state test, for doses of controlled release 20 mg tablets and immediate release 10 mg tablets of oxymorphone. The figure shows the plasma concentrations after the final controlled release tablet is given on Day 9, and the final immediate release tablet is given 12 hours thereafter. The steady state administration of the controlled release tablets clearly shows a steady moderate level of oxymorphone ranging from just over 1 ng/ml to almost 1.75 ng/ml over the course of a twelve hour period, where the immediate release tablet shows wide variations in blood plasma concentration. Table 20 shows the levels of oxymorphone and 6-hydroxyoxymorphone from FIG. 10 in tabular form.

TABLE 20

Summary of Mean Plasma Concentration (ng/ml)

		Oxymorphone		6-Hydroxyoxymorphone	
Day	Hour	Controlled Release 20 mg	Immediate Release 10 mg	Controlled Release 20 mg	Immediate Release 10 mg
4	0.00	1.10	0.75	0.89	0.72
5	0.00	1.12	0.84	1.15	0.88
6	0.00	1.20	0.92	1.15	0.87
7	0.00	1.19	0.91	1.27	1.00
8	0.00	1.19	0.86	1.29	0.98
9	0.00	1.03	1.07	1.09	1.05
	0.25		2.64		1.70
	0.50		3.12	1.50	2.09
	1.00		2.47	1.70	1.68
	1.50		2.05	1.63	1.55
	2.00		1.78	1.64	1.30
	3.00		1.27	1.47	1.11
	4.00		0.98	1.39	0.98
	5.00		1.01	1.21	0.89
	6.00		0.90	1.06	0.84
	6.25		1.17		0.88

TABLE 20-continued

Summary of Mean Plasma Concentration (ng/ml)

		Oxymorphone		6-Hydroxyoxymorphone	
Day	Hour	Controlled Release 20 mg	Immediate Release 10 mg	Controlled Release 20 mg	Immediate Release 10 mg
	6.50		1.88		1.06
	7.00		2.12		1.20
	7.50		2.24		1.15
	8.00	1.32	2.01	0.97	1.03
	9.00		1.52		0.90
	10.0	1.32	1.24	0.85	0.84
	11.0		1.11		0.74
	12.0	1.18	0.96	0.79	0.70

TABLE 21

Mean Single-Dose Pharmacokinetic Results

	Controlled Release 20 mg		Immediate Release 10 mg	
	oxy-morphone	6-OH-oxymorphone	oxymor-phone	6-OH-oxymorphone
$AUC_{(o-t)}$	14.74	11.54	7.10	5.66
$AUC_{(o-inf)}$	15.33	16.40	7.73	8.45
C_{max}(ng/ml)	1.12	0.68	1.98	1.40
T_{max}(hr)	5.00	2.00	0.50	0.50
T½ (hr)	9.25	26.09	10.29	29.48

Parent 6-OH oxymorphone $AUC_{(o-t)}$ values were lower than the parent compound after administration of either dosage form, but the $AUC_{(o-inf)}$ values are slightly higher due to the longer half-life for the metabolite. This relationship was similar for both the immediate-release (IR) and controlled release (CR) dosage forms. As represented by the average plasma, concentration graph, the CR dosage form has a significantly longer time to peak oxymorphone concentration and a lower peak oxymorphone concentration. The 6-OH oxymorphone peak occurred sooner than the parent peak following the CR dosage form, and simultaneously with the parent peak following the IR dosage form.

It is important to note that while the present invention is described and exemplified, using 20 mg tablets, the invention may also be used with other strengths of tablets. In each strength, it is important to note how a 20 mg tablet of the same composition (except for the change in strength) would act. The blood plasma levels and pain intensity information are provided for 20 mg tablets, however the present invention is also intended to encompass 5 to 80 mg controlled release tablets. For this reason, the blood plasma level of oxymorphone or 6-hydroxyoxymorphone in nanograms per milliliter of blood, per mg oxymorphone (ng/mg·ml) administered is measured. Thus at 0.02 ng/mg·ml, a 5 mg tablet should produce a minimum blood plasma concentration of 0.1 ng/ml. A stronger tablet will produce a higher blood plasma concentration of active molecule, generally proportionally. Upon administration of a higher dose tablet, for example 80 mg, the blood plasma level of oxymorphone and 6-OH oxymorphone may more than quadruple compared to a 20 mg dose, although conventional treatment of low bioavailability substances would lead away from this conclusion. If this is the case, it may be because the body can only process a limited amount oxymorphone at one time. Once the bolus is processed, the blood level of oxymorphone returns to a proportional level.

It is the knowledge that controlled release oxymorphone tablets are possible to produce and effective to use, which is most important, made possible with the high bioavailability of oxymorphone in a controlled release tablet. This also holds true for continuous periodic administration of controlled release formulations. The intent of a controlled release opioid formulation is the long-term management of pain. Therefore, the performance of a composition when administered periodically (one to three times per day) over several days is important. In such a regime, the patient reaches a "steady state" where continued administration will produce the same results, when measured by duration of pain relief and blood plasma levels of pharmaceutical. Such a test is referred to as a "steady state" test and may require periodic administration over an extended time period ranging from several days to a week or more. Of course, since a patient reaches steady state in such a test, continuing the test for a longer time period should not affect the results. Further, when testing blood plasma levels in such a test, if the time period for testing exceeds the interval between doses, it is important the regimen be stopped after the test is begun so that observations of change in blood level and pain relief may be made without a further dose affecting these parameters.

Study 5—Controlled Release 40 mg vs. Immediate Release 4.times.10 mg under Fed and Fasting Conditions

The objectives of this study were to assess the relative bioavailability of oxymorphone from oxymorphone controlled release (40 mg) compared to oxymorphone immediate release (4.times. 10 mg) under both fasted and fed conditions, and to determine the effect of food on the bioavailability of oxymorphone from the controlled release formulation, oxymorphone CR, and from the immediate release formulation, oxymorphone IR.

This study had a single-center, open-label, analytically blinded, randomized, four-way crossover design. Subjects randomized to Treatment 5A and Treatment 5C, as described below, were in a fasted state following a 10-hour overnight fast. Subjects randomized to Treatment 5B and Treatment 5D, as described below, were in the fed state, having had a high fat meal, completed ten minutes prior to dosing. There was a 14-day washout interval between the four dose administrations. The subjects were confined to the clinic during each study period. Subject assigned to receive Treatment 5A and Treatment 5B were discharged from the clinic on Day 3 following the 48-hour procedures, and subjects assigned to receive Treatment 5C and Treatment 5D were discharged from the clinic on Day 2 following the 36-hour procedures. On Day 1 of each study period the subjects received one of four treatments:

Treatments 5A and 5B: Oxymorphone controlled release 40 mg tablets from Table 2. Subjects randomized to Treatment 5A received a single oral dose of one 40 mg oxymorphone controlled release tablet taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 5B received a single oral dose of one 40 mg oxymorphone controlled release tablet taken with 240 ml of water 10 minutes after a standardized high fat meal.

Treatments 5C and 5D: Immediate release tablet (IR) 4.times.10 mg Oxymorphone. Subjects randomized to Treatment 5C received a single oral dose of 4.times.10 mg oxymorphone IR tablet taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 5D received a single oral dose of 4.times.10 mg oxymorphone IR tablet taken with 240 ml of water 10 minutes after a standardized high-fat meal.

A total of 28 male subjects were enrolled in the study, and 25 subjects completed the study. A total of 28 subjects received at least one treatment. Only subjects who completed all 4 treatments were included in the summary statistics and statistical analysis.

Blood samples (7 ml) were collected during each study period at the 0 hour (predose), and at 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 60, and 72 hours post-dose (19 samples) for subjects randomized to all Treatments.

The mean oxymorphone plasma concentration versus time is presented in Table 22. The arithmetic means of the plasma oxymorphone pharmacokinetic parameters and the statistics for all Treatments are summarized in Table 23.

TABLE 22

Mean Plasma Concentration vs. Time (ng/ml)

Time (hr)	Treatment 5A	Treatment 5B	Treatment 5C	Treatment 5D
0	0.00	0.00	0.00	0.00
0.25	0.47	0.22	3.34	1.79
0.50	1.68	0.97	7.28	6.59
0.75	1.92	1.90	6.60	9.49
1	2.09	2.61	6.03	9.91
1.5	2.18	3.48	4.67	8.76
2	2.18	3.65	3.68	7.29
3	2.00	2.86	2.34	4.93
4	1.78	2.45	1.65	3.11
5	1.86	2.37	1.48	2.19
6	1.67	2.02	1.28	1.71
8	1.25	1.46	0.92	1.28
10	1.11	1.17	0.78	1.09
12	1.34	1.21	1.04	1.24
24	0.55	0.47	0.40	0.44
36	0.21	0.20	0.16	0.18
48	0.06	0.05	0.04	0.05
60	0.03	0.01	0.01	0.01
72	0.00	0.00	0.00	0.00

TABLE 23

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 5

	Treatment 5A		Treatment 5B		Treatment 5C		Treatment 5D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max}	2.79	0.84	4.25	1.21	9.07	4.09	12.09	5.42
T_{max}	2.26	2.52	1.96	1.06	0.69	0.43	1.19	0.62
$AUC_{(o-t)}$	35.70	10.58	38.20	11.04	36.00	12.52	51.35	20.20
$AUC_{(o-Inf)}$	40.62	11.38	41.17	10.46	39.04	12.44	54.10	20.26
$T_{1/2el}$	12.17	7.57	10.46	5.45	11.65	6.18	9.58	3.63

The relative bioavailability calculations are summarized in Tables 24 and 25.

TABLE 24

Relative Bioavailability Determination Based on $AUC_{(o-Inf)}$

F_{rel} (5D vs. 5C)	F_{rel} (5B vs. 5A)
1.3775	1.0220

TABLE 25

Relative bioavailability Determination Based on $AUC_{(o-24)}$

F_{rel} (5D vs. 5C)	F_{rel} (5B vs. 5A)
1.4681	1.0989

The mean 6-OH oxymorphone plasma concentration versus time is presented in Table 26.

TABLE 26

Mean Plasma Concentration vs. Time (ng/ml) 6-Hydroxyoxymorphone

Time (hr)	Treatment 5A	Treatment 5B	Treatment 5C	Treatment 5D
0	0.00	0.00	0.00	0.00
0.25	0.27	0.05	2.36	0.50
0.50	1.32	0.31	5.35	1.98
0.75	1.37	0.59	4.53	2.97
1	1.44	0.82	3.81	2.87
1.5	1.46	1.09	2.93	2.58
2	1.46	1.28	2.37	2.29
3	1.39	1.14	1.69	1.72
4	1.25	1.14	1.33	1.26
5	1.02	1.00	1.14	1.01
6	0.93	0.86	0.94	0.86
8	0.69	0.72	0.73	0.77
10	0.68	0.67	0.66	0.75
12	0.74	0.66	0.70	0.77
24	0.55	0.52	0.54	0.61
36	0.23	0.30	0.28	0.27
48	0.18	0.20	0.20	0.19
60	0.09	0.10	0.09	0.09
72	0.06	0.06	0.04	0.05

TABLE 27

Pharmacokinetic Parameters of Plasma 6-Hydroxyoxymorphone for Study 5

	Treatment 5A		Treatment 5B		Treatment 5C		Treatment 5D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max}	1.88	0.69	1.59	0.63	6.41	3.61	3.79	1.49
T_{max}	1.48	1.18	2.73	1.27	0.73	0.47	1.18	0.74
$AUC_{(o-t)}$	28.22	10.81	26.95	11.39	33.75	10.29	32.63	13.32
$AUC_{(o-inf)}$	33.15	11.25	32.98	10.68	37.63	17.01	36.54	13.79
$T_{1/2el}$	17.08	7.45	21.92	8.41	16.01	6.68	16.21	7.42

The above description incorporates preferred embodiments and examples as a means of describing and enabling the invention to be practiced by one of skill in the art. It is imagined that changes can be made without departing from the spirit and scope of the invention described herein and defined in the appended claims.

We claim:

1. An analgesically effective controlled release pharmaceutical composition with a twelve hour dosing interval in the form of a tablet, comprising oxymorphone or a pharmaceutically acceptable salt thereof as the sole active ingredient in the tablet, and a controlled release delivery system comprising at least one pharmaceutical excipient, wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.

2. The pharmaceutical composition of claim 1 wherein about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 4 hours in the test.

3. The pharmaceutical composition of claim 1 wherein at least about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test.

4. The pharmaceutical composition of claim 1 wherein the controlled release delivery system comprises a hydrophilic material that forms a gel upon exposure to gastrointestinal fluid.

5. The pharmaceutical composition of claim 1 wherein the controlled release delivery system comprises a heteropolysaccharide and an agent capable of cross-linking the heteropolysaccharide in presence of gastrointestinal fluid.

6. The pharmaceutical composition of claim 5 wherein the heteropolysaccharide and the agent capable of cross-linking the heteropolysaccharide are present in a weight ratio of about 1:3 to about 3:1.

7. The pharmaceutical composition of claim 5 wherein the heteropolysaccharide comprises xanthan gum or deacylated xanthan gum.

8. The pharmaceutical composition of claim 5 wherein the agent capable of cross-linking the heteropolysaccharide comprises a homopolysaccharide gum.

9. The pharmaceutical composition of claim 8 wherein the homopolysaccharide gum comprises locust bean gum.

10. The pharmaceutical composition of claim 1 wherein the controlled release delivery system further comprises a hydrophobic polymer.

11. The pharmaceutical composition of claim 10 wherein the hydrophobic polymer comprises an alkylcellulose.

12. The pharmaceutical composition of claim 8 further comprising a cationic cross-linking agent.

13. The pharmaceutical composition of claim 12 wherein the cationic cross-linking agent is selected from calcium sulfate, sodium chloride, potassium sulfate, sodium carbonate, lithium chloride, tripotassium phosphate, sodium borate, potassium bromide, potassium fluoride, sodium bicarbonate, calcium chloride, magnesium chloride, sodium citrate, sodium acetate, calcium lactate, magnesium sulfate, sodium fluoride, and combinations thereof.

14. The pharmaceutical composition of claim 13 wherein the cationic cross-linking agent is present in an amount of about 0.5% to about 16%, by weight of the composition.

15. The pharmaceutical composition of claim 5 wherein the weight ratio of heteropolysaccharide to oxymorphone or pharmaceutically acceptable salt thereof is about 10:1 to about 1:10.

16. The pharmaceutical composition of claim 1 wherein oxymorphone or pharmaceutically acceptable salt thereof is present in an amount of about 5 mg to about 80 mg.

17. The pharmaceutical composition of claim 5 wherein the controlled release delivery system comprises about 10% to about 99% of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum, about 1% to about 20% of a cationic crosslinking agent, and about 0% to about 89% of other ingredients which qualify as an inert pharmaceutical diluent, by total weight of the controlled release delivery system.

18. A method of treating pain in a subject in need thereof, the method comprising administering to the subject the pharmaceutical composition of claim 1 comprising about 5 mg to about 80 mg of oxymorphone or pharmaceutically acceptable salt thereof.

19. An analgesically effective controlled release pharmaceutical composition with a twelve hour dosing interval in the form of a tablet, comprising oxymorphone or pharmaceutically acceptable salt thereof as the sole active ingredient in the tablet and a controlled release delivery system comprising a hydrophilic material that forms a gel upon exposure to gastrointestinal fluid, wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8

at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the composition at about 1 hour in the test, about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the composition at about 4 hours in the test, and at least about 80%, by weight, of the oxymorphone or salt thereof is released from the composition at about 10 hours in the test.

20. The method of claim **18** wherein upon oral administration of the composition the oxymorphone $AUC_{(o-inf)}$ is no more than 20% higher when the composition is administered to the subject under fed as compared to fasted conditions.

* * * * *

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Kao et al.

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(45) Date of Patent: *Dec. 11, 2012

(54) **OXYMORPHONE CONTROLLED RELEASE FORMULATIONS**

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This patent is subject to a terminal disclaimer.

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(58) **Field of Classification Search** ..... None
See application file for complete search history.

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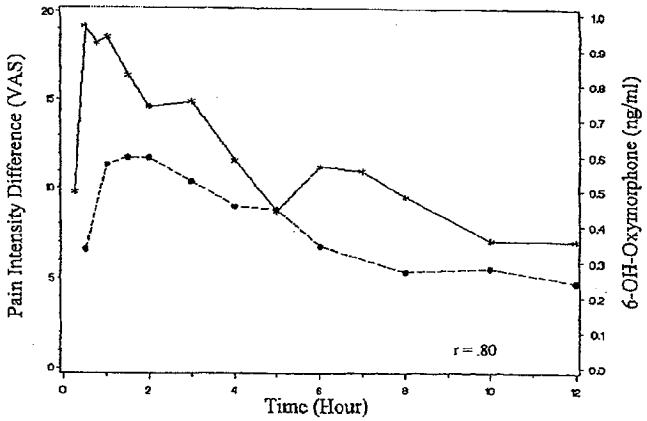
(57) **ABSTRACT**

The invention pertains to a method of relieving pain by administering a controlled release pharmaceutical tablet containing oxymorphone which produces a mean minimum blood plasma level 12 to 24 hours after dosing, as well as the tablet producing the sustained pain relief.

82 Claims, 10 Drawing Sheets

PK Profile for 6-OH-Oxymorphone with PID Scores



* Pain Intensity Difference • 6-OH-Oxymorphone Plasma Concentrations

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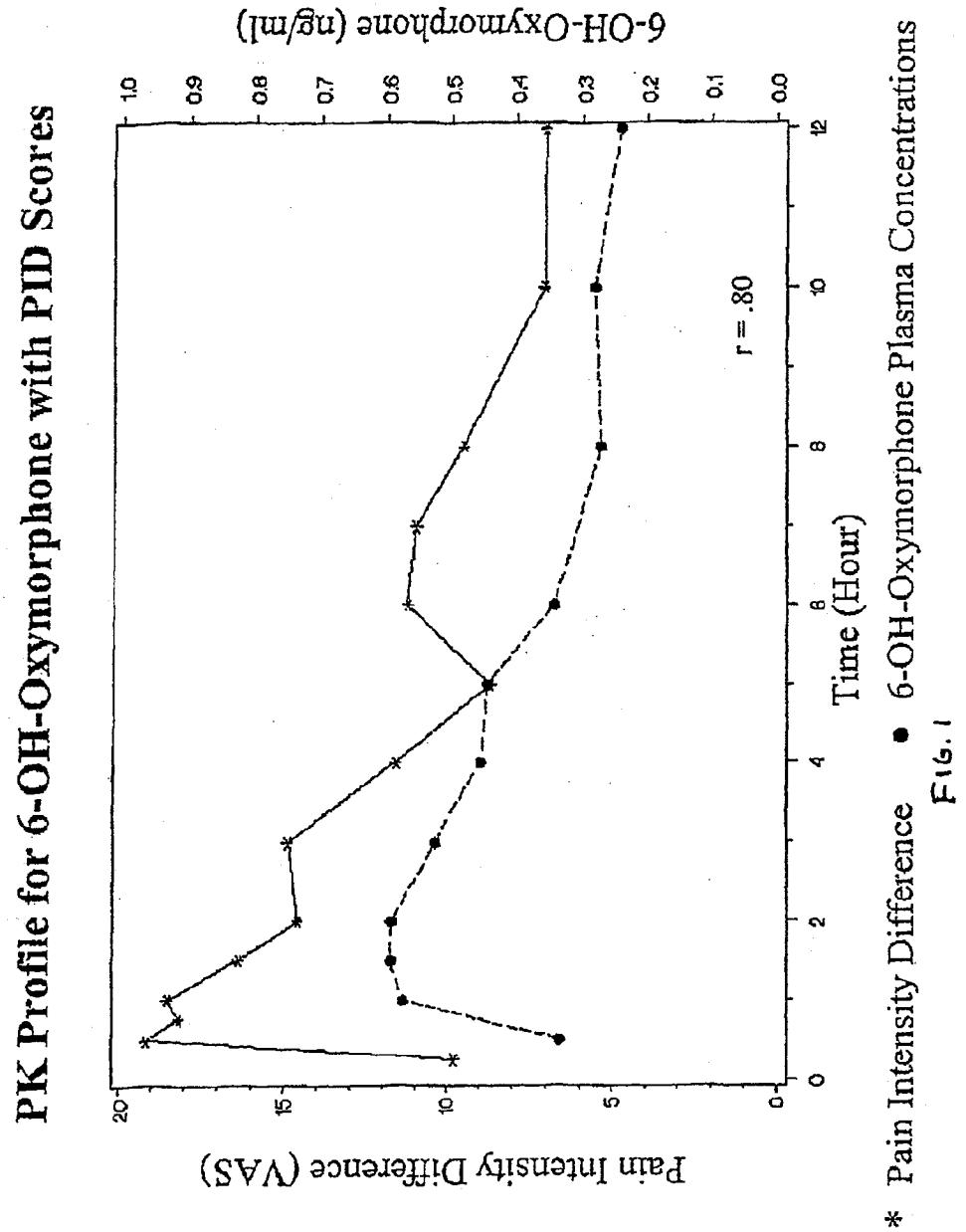
PK Profile for 6-OH-Oxymorphone with PID Scores
6-OH-Oxymorphone (ng/ml)
Pain Intensity Difference (VAS)
Time (Hour)
r = .80
* Pain Intensity Difference • 6-OH-Oxymorphone Plasma Concentrations

F16. 1

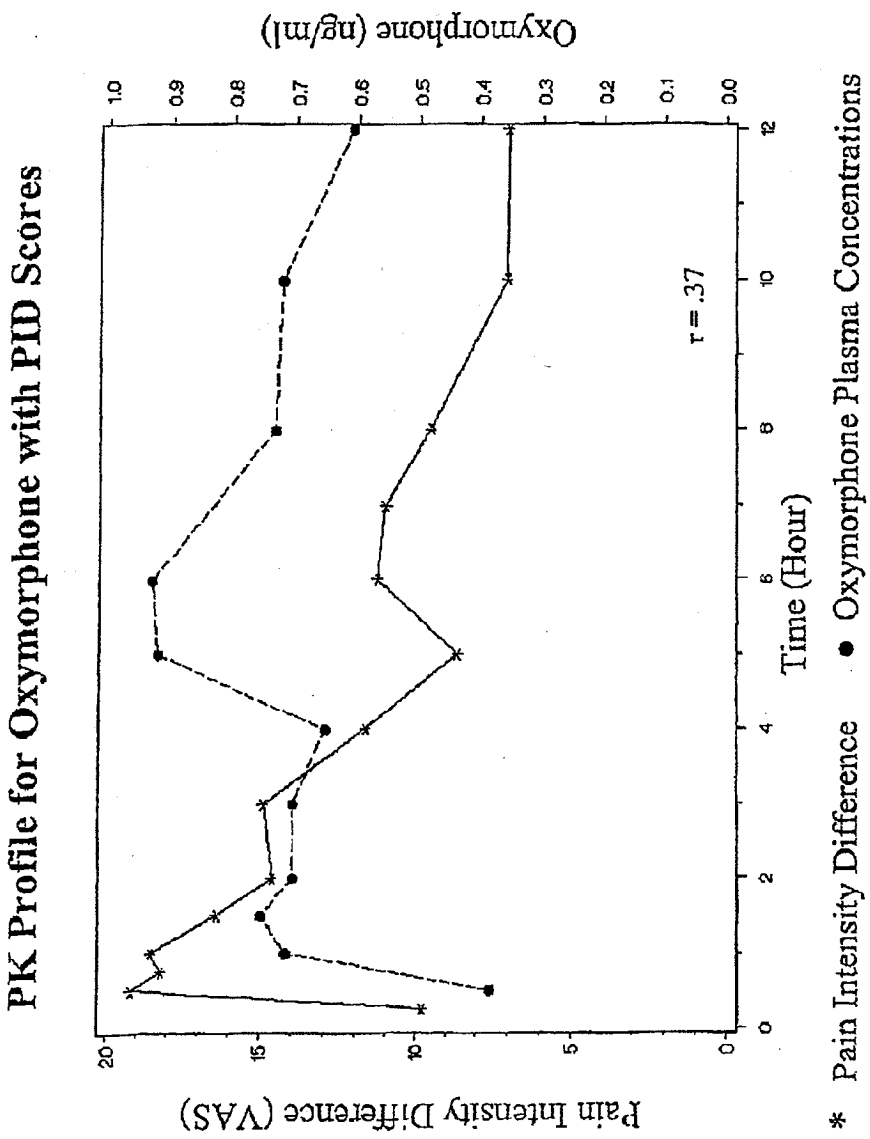
PK Profile for Oxymorphone with PID Scores
Pain Intensity Difference (VAS)
Oxymorphone (ng/ml)
Time (Hour)
r = .37
* Pain Intensity Difference
● Oxymorphone Plasma Concentrations

FIG. 2

PK Profile for 6-OH-Oxymorphone with Categorical Pain Scores

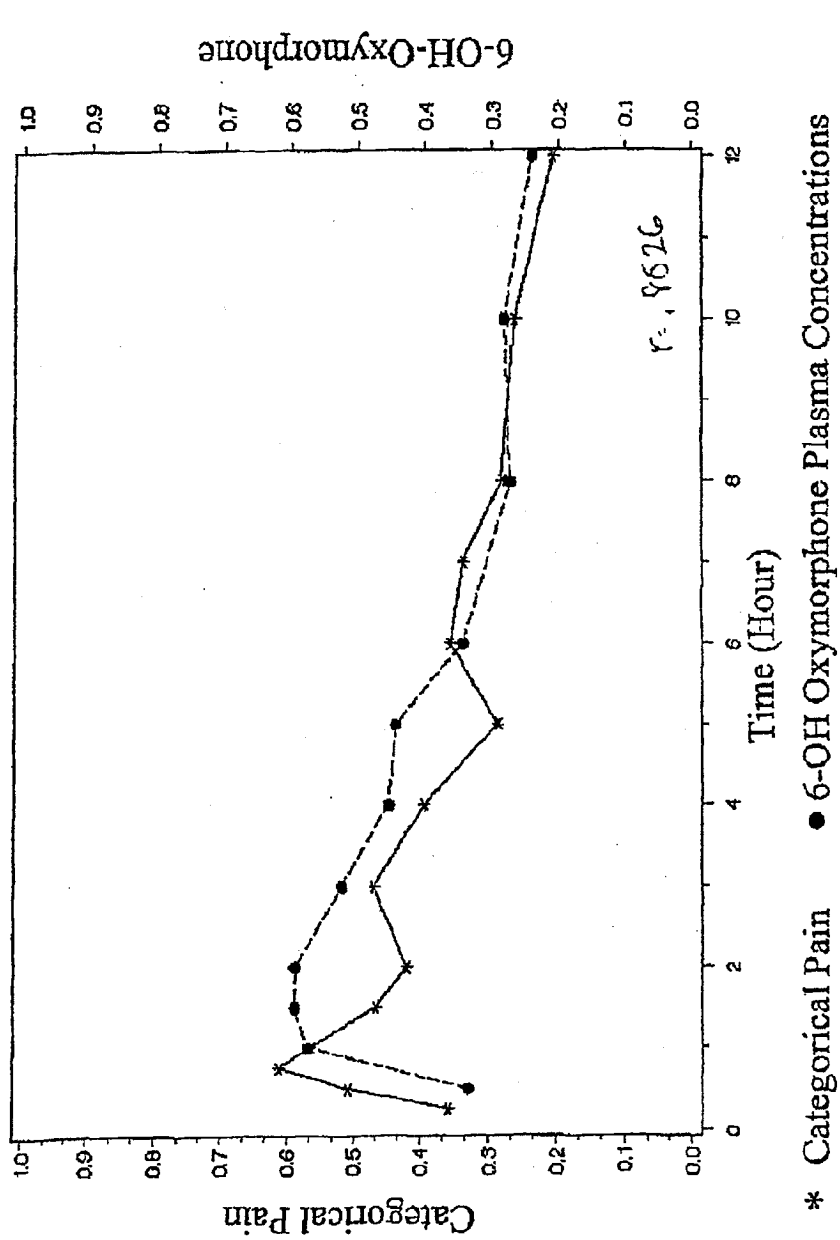

FIG. 3

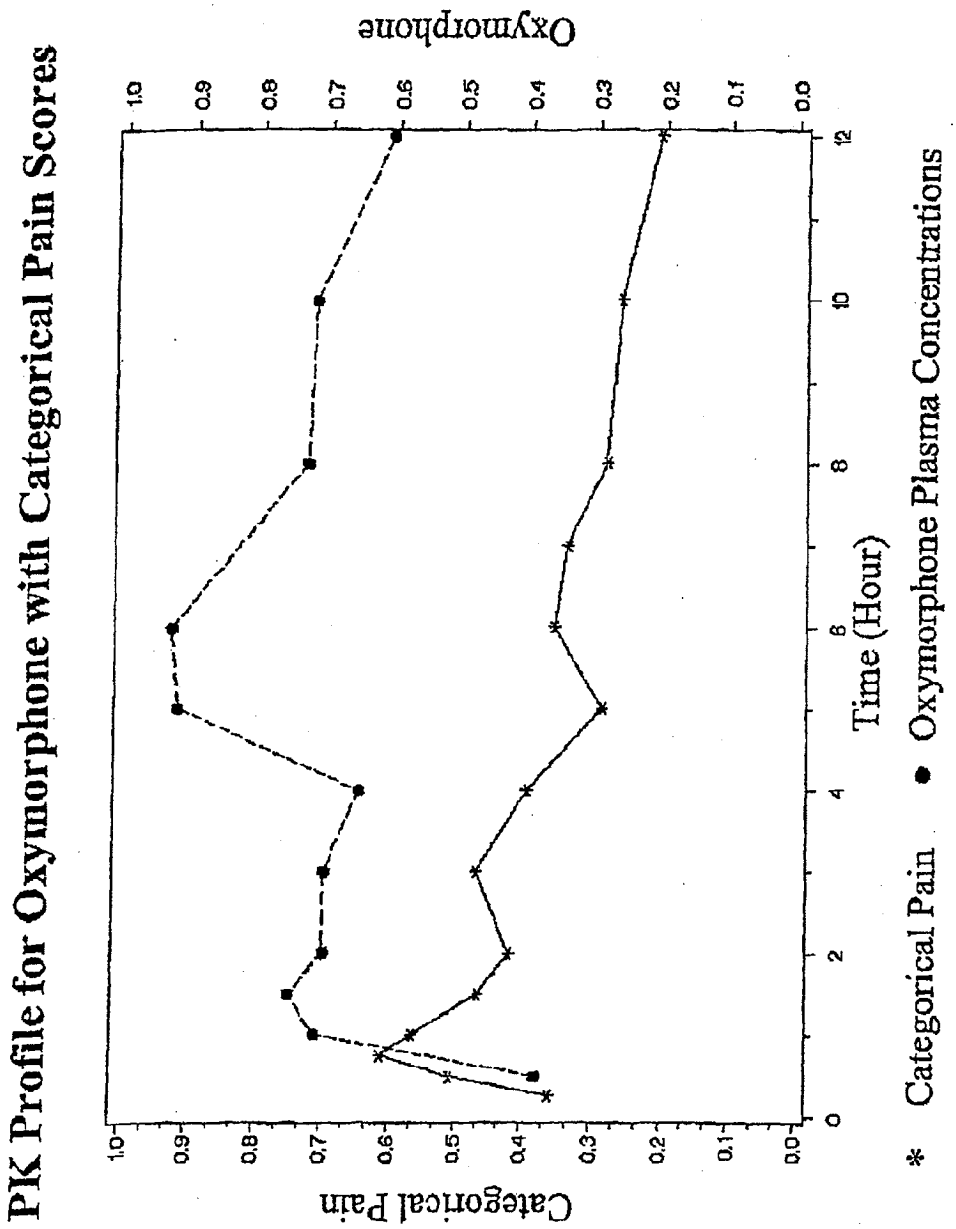
PK Profile for Oxymorphone with Categorical Pain Scores
Oxymorphone
Categorical Pain
Time (Hour)
* Categorical Pain
• Oxymorphone Plasma Concentrations

Fig. 4

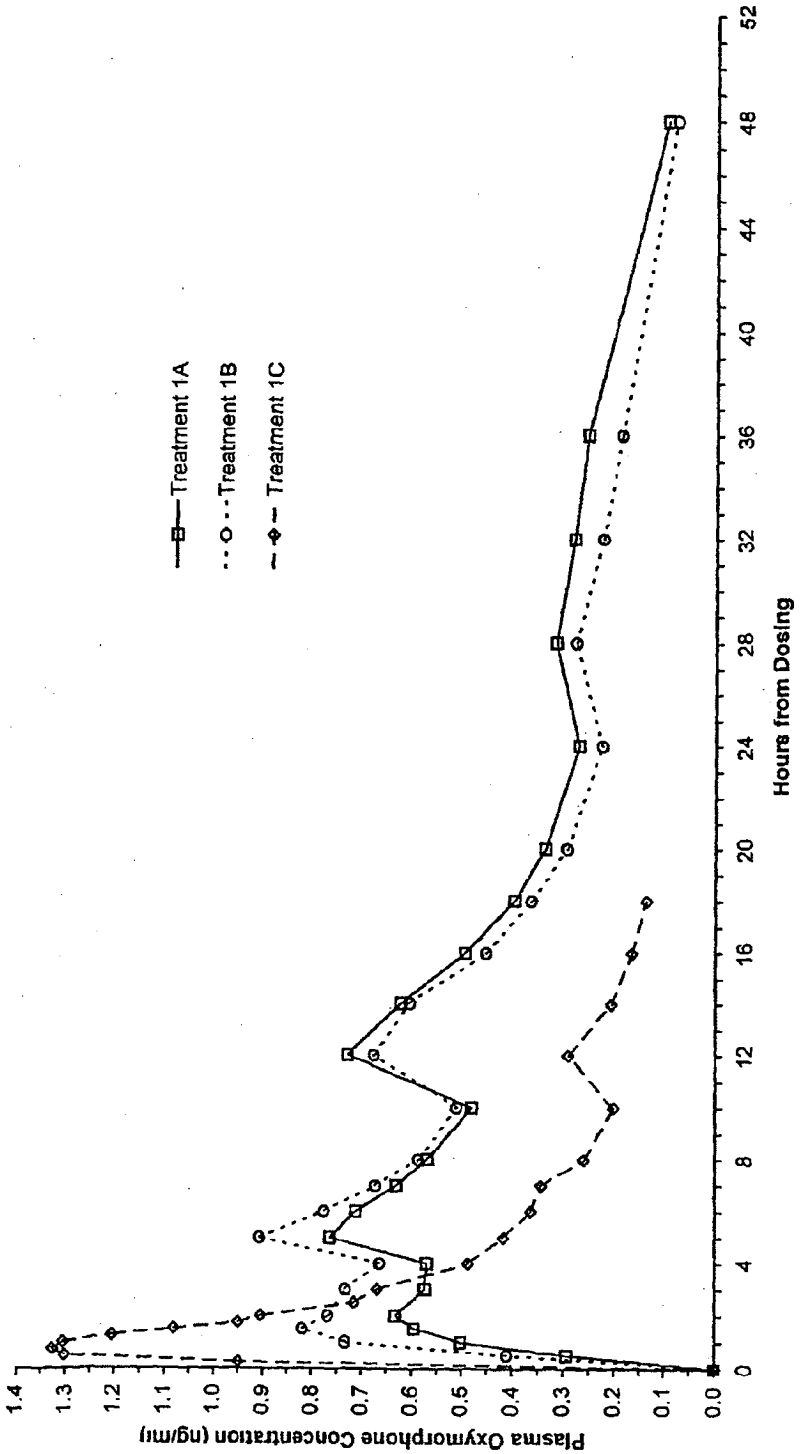
Treatment 1A
Treatment 1B
Treatment 1C
Plasma Oxymorphone Concentration (ng/ml)
Hours from Dosing
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
0
4
8
12
16
20
24
28
32
36
40
44
48
52

Figure 5

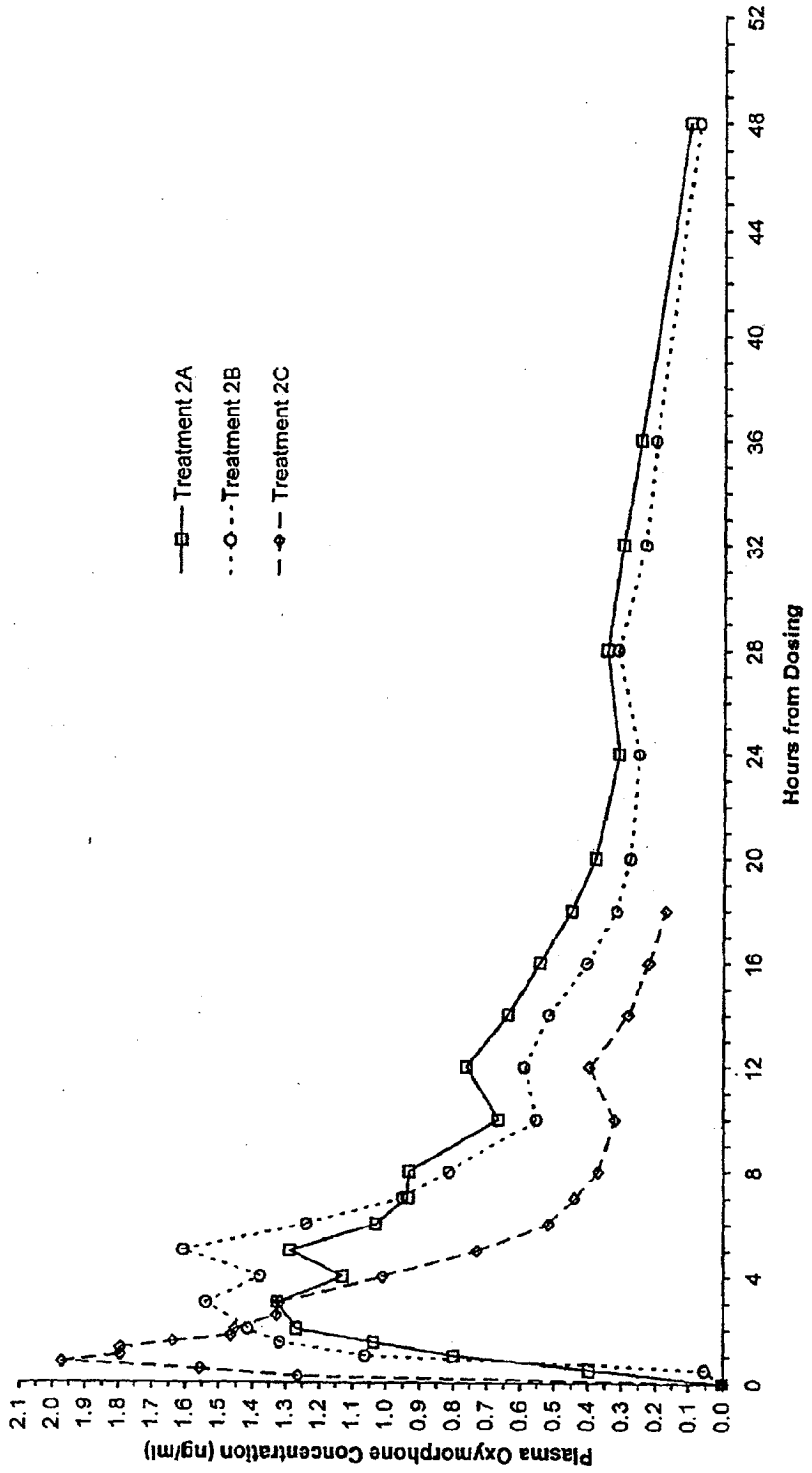
Treatment 2A
Treatment 2B
Treatment 2C
Plasma Oxymorphone Concentration (ng/ml)
Hours from Dosing
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
1.6
1.7
1.8
1.9
2.0
2.1
0
4
8
12
16
20
24
28
32
36
40
44
48
52

Figure 6

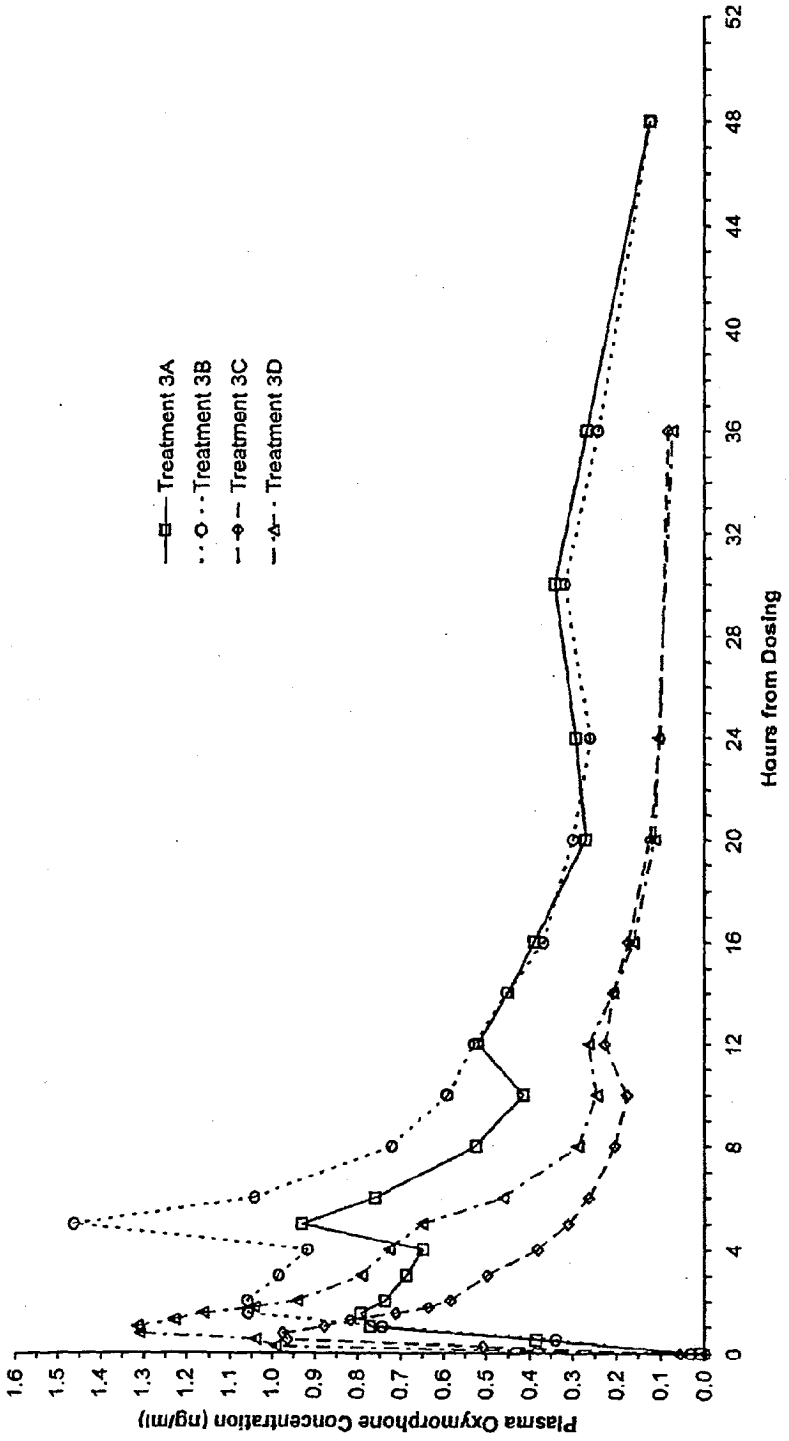
Treatment 3A
Treatment 3B
Treatment 3C
Treatment 3D
Plasma Oxymorphone Concentration (ng/ml)
Hours from Dosing
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
1.6
0
4
8
12
16
20
24
28
32
36
40
44
48
52

Figure 7

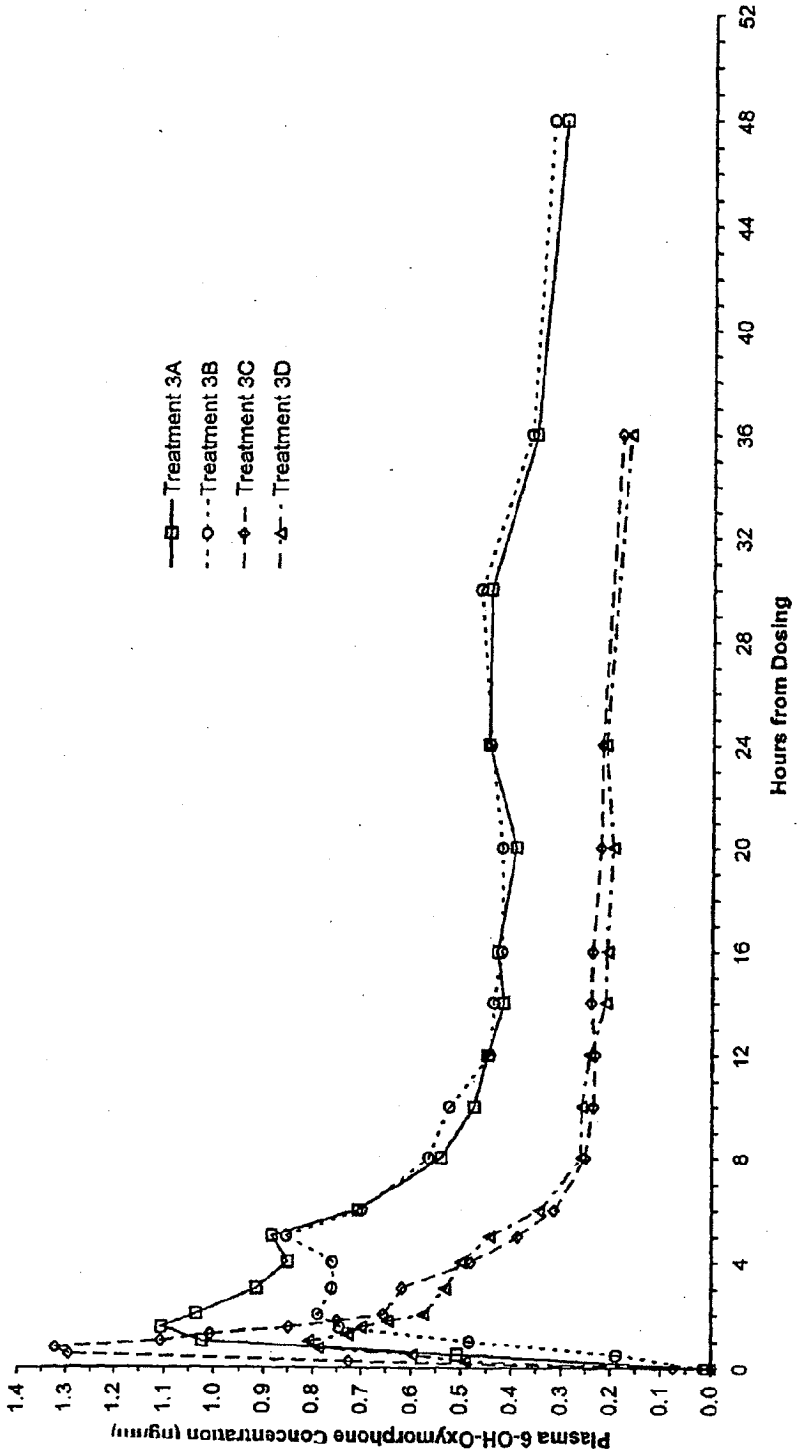
Treatment 3A
Treatment 3B
Treatment 3C
Treatment 3D
Plasma 6-OH-Oxymorphone Concentration (ng/mL)
Hours from Dosing
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
0
4
8
12
16
20
24
28
32
36
40
44
48
52

Figure 8

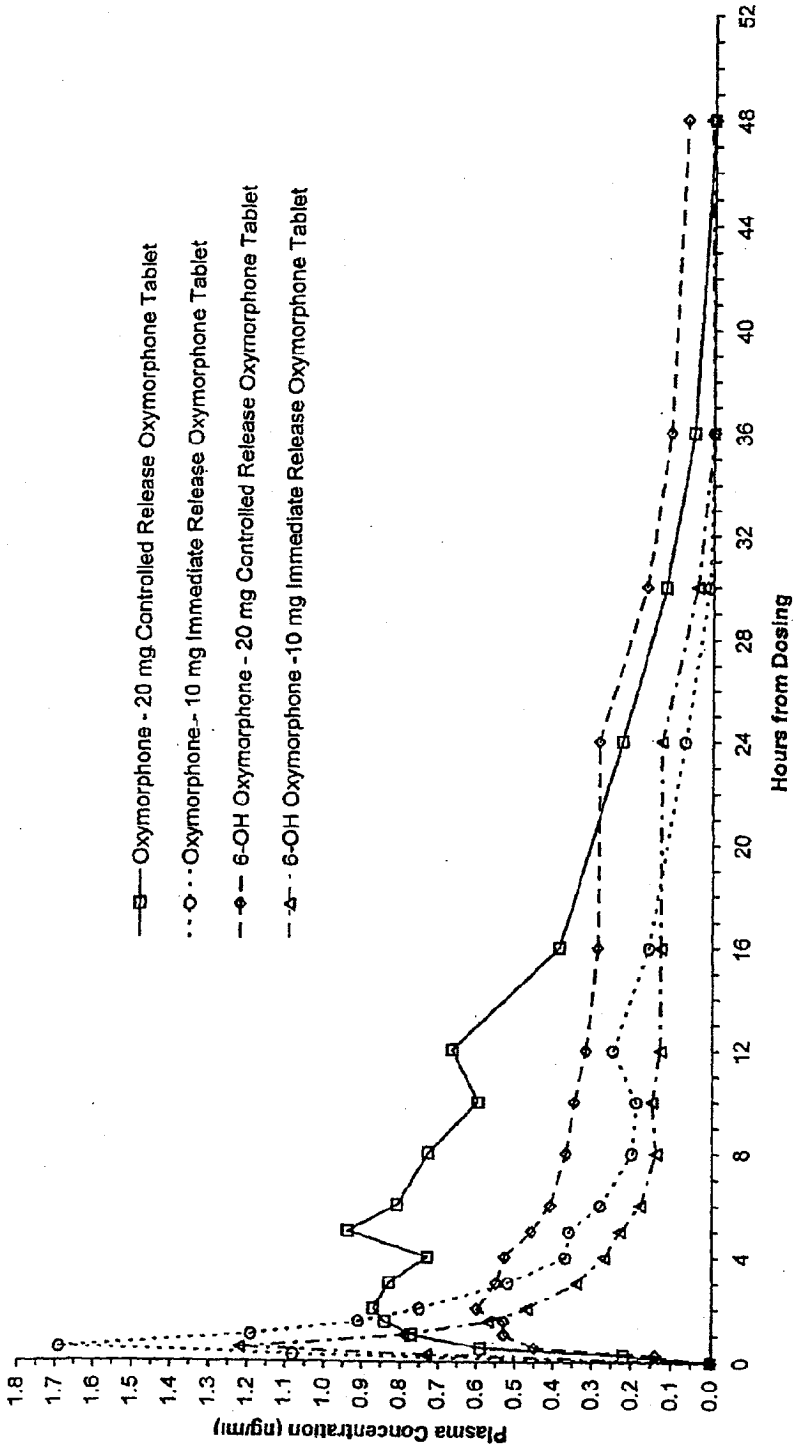
Oxymorphone - 20 mg Controlled Release Oxymorphone Tablet
Oxymorphone - 10 mg Immediate Release Oxymorphone Tablet
6-OH Oxymorphone - 20 mg Controlled Release Oxymorphone Tablet
6-OH Oxymorphone -10 mg Immediate Release Oxymorphone Tablet
Plasma Concentration (ng/ml)
Hours from Dosing
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
1.6
1.7
1.8
0
4
8
12
16
20
24
28
32
36
40
44
48
52

Figure 9

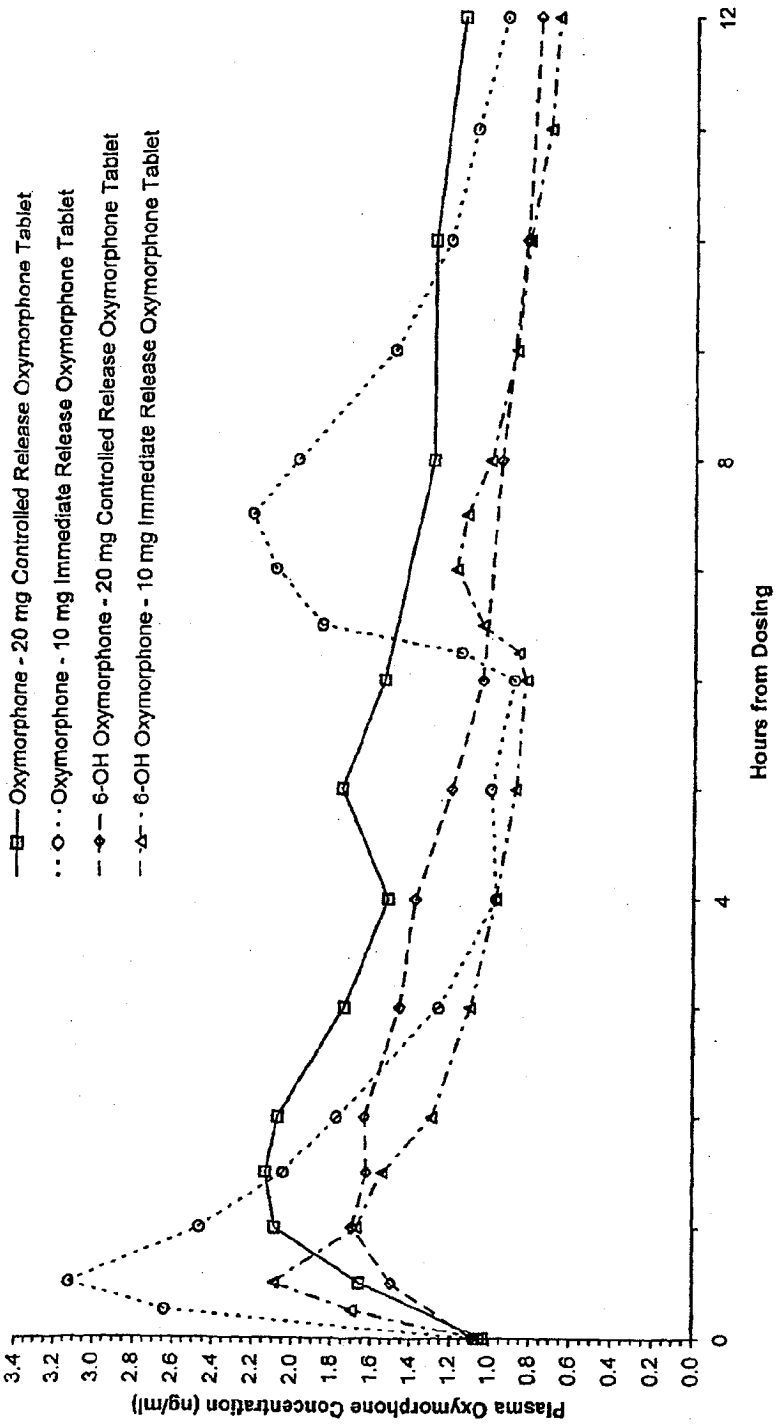
Oxymorphone - 20 mg Controlled Release Oxymorphone Tablet
Oxymorphone - 10 mg Immediate Release Oxymorphone Tablet
6-OH Oxymorphone - 20 mg Controlled Release Oxymorphone Tablet
6-OH Oxymorphone - 10 mg Immediate Release Oxymorphone Tablet
Plasma Oxymorphone Concentration (ng/ml)
Hours from Dosing
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
0
4
8
12

Figure 10

OXYMORPHONE CONTROLLED RELEASE FORMULATIONS

RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 10/190,192 filed Jul. 3, 2002 and claims priority to U.S. Provisional Patent Application Ser. Nos. 60/329,445 filed Oct. 15, 2001, 60/329,432 filed Oct. 15, 2001, 60/303,357 filed Jul. 6, 2001, and 60/329,444 filed Oct. 15, 2001, which are incorporated herein by reference to the extent permitted by law.

BACKGROUND OF THE INVENTION

Pain is the most frequently reported symptom and it is a common clinical problem which confronts the clinician. Many millions of people in the USA suffer from severe pain that, according to numerous recent reports, is chronically undertreated or inappropriately managed. The clinical usefulness of the analgesic properties of opioids has been recognized for centuries, and morphine and its derivatives have been widely employed for analgesia for decades in a variety of clinical pain states.

Oxymorphone HCl (14-hydroxydihydromorphinone hydrochloride) is a semi-synthetic phenanthrene-derivative opioid agonist, widely used in the treatment of acute and chronic pain, with analgesic efficacy comparable to other opioid analgesics. Oxymorphone is currently marketed as an injection (1 mg/ml in 1 ml ampules; 1.5 mg/ml in 1 ml ampules; 1.5 mg/ml in 10 ml multiple dose vials) for intramuscular, subcutaneous, and intravenous administration, and as 5 mg rectal suppositories. At one time, 2 mg, 5 mg and 10 mg oral immediate release (IR) tablet formulations of oxymorphone HCl were marketed. Oxymorphone HCl is metabolized principally in the liver and undergoes conjugation with glucuronic acid and reduction to 6-alpha- and beta-hydroxy epimers.

An important goal of analgesic therapy is to achieve continuous relief of chronic pain. Regular administration of an analgesic is generally required to ensure that the next dose is given before the effects of the previous dose have worn off. Compliance with opioids increases as the required dosing frequency decreases. Non-compliance results in suboptimal pain control and poor quality of life outcomes. (Ferrell B et al. Effects of controlled-release morphine on quality of life for cancer pain. *Oncol. Nur. Forum* 1989; 4:521-26). Scheduled, rather than "as needed" administration of opioids is currently recommended in guidelines for their use in chronic non-malignant pain. Unfortunately, evidence from prior clinical trials and clinical experience suggests that the short duration of action of immediate release oxymorphone would necessitate administration every 4-6 hours in order to maintain optimal levels of analgesia in chronic pain. A controlled release formulation which would allow less frequent dosing of oxymorphone would be useful in pain management.

For instance, a controlled release formulation of morphine has been demonstrated to provide patients fewer interruptions in sleep, reduced dependence on caregivers, improved compliance, enhanced quality of life outcomes, and increased control over the management of pain. In addition, the controlled release formulation of morphine was reported to provide more constant plasma concentration and clinical effects, less frequent peak to trough fluctuations, reduced dosing frequency, and possibly fewer side effects. (Thirlwell M P et al., Pharmacokinetics and clinical efficacy of oral morphine solution and controlled-release morphine tablets in cancer patients. *Cancer* 1989; 63:2275-83; Goughnour B R et al., Analgesic response to single and multiple doses of controlled-release morphine tablets and morphine oral solution in cancer patients. *Cancer* 1989; 63:2294-97; Ferrell B. et al., Effects of controlled-release morphine on quality of life for cancer pain. *Oncol. Nur. Forum* 1989; 4:521-26.

There are two factors associated with the metabolism of some drugs that may present problems for their use in controlled release systems. One is the ability of the drug to induce or inhibit enzyme synthesis, which may result in a fluctuating drug blood plasma level with chronic dosing. The other is a fluctuating drug blood level due to intestinal (or other tissue) metabolism or through a hepatic first-pass effect.

Oxymorphone is metabolized principally in the liver, resulting in an oral bioavailability of about 10%. Evidence from clinical experience suggests that the short duration of action of immediate release oxymorphone necessitates a four hour dosing schedule to maintain optimal levels of analgesia. It would be useful to clinicians and patients alike to have controlled release dosage forms of oxymorphone to use to treat pain and a method of treating pain using the dosage forms.

SUMMARY OF THE INVENTION

The present invention provides methods for relieving pain by administering a controlled release pharmaceutical tablet containing oxymorphone which produces at least a predetermined minimum blood plasma level for at least 12 hours after dosing, as well as tablets that produce the sustained pain relief over this time period.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a pharmacokinetic profile for 6-hydroxy oxymorphone with PID scores.

FIG. **2** is a pharmacokinetic profile for oxymorphone with PID scores.

FIG. **3** is a pharmacokinetic profile for 6-hydroxy oxymorphone with categorical pain scores.

FIG. **4** is a pharmacokinetic profile for oxymorphone with categorical pain scores.

FIG. **5** is a graph of the mean blood plasma concentration of oxymorphone versus time for clinical study 1.

FIG. **6** is a graph of the mean blood plasma concentration of oxymorphone versus time for clinical study 2.

FIG. **7** is a graph of the mean blood plasma concentration of oxymorphone versus time for clinical study 3.

FIG. **8** is a graph of the mean blood plasma concentration of 6-hydroxy oxymorphone versus time for clinical study 3.

FIG. **9** is a graph of the mean blood plasma concentration of oxymorphone for immediate and controlled release tablets from a single dose study.

FIG. **10** is a graph of the mean blood plasma concentration of oxymorphone for immediate and controlled release tablets from a steady state study.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides methods for alleviating pain for 12 to 24 hours using a single dose of a pharmaceutical composition by producing a blood plasma level of oxymorphone and/or 6-OH oxymorphone of at least a minimum value for at least 12 hours or more. As used herein, the terms "6-OH oxymorphone" and "6-hydroxy oxymorphone" are interchangeable and refer to the analog of oxymorphone hav-

ing an alcohol (hydroxy) moiety that replaces the carboxy moiety found on oxymorphone at the 6-position.

To overcome the difficulties associated with a 4-6 hourly dosing frequency of oxymorphone, this invention provides an oxymorphone controlled release oral solid dosage form, comprising a therapeutically effective amount of oxymorphone or a pharmaceutically acceptable salt of oxymorphone. It has been found that the decreased rate of release of oxymorphone from the oral controlled release formulation of this invention does not substantially decrease the bioavailability of the drug as compared to the same dose of a solution of oxymorphone administered orally. The bioavailability is sufficiently high and the release rate is such that a sufficient plasma level of oxymorphone and/or 6-OH oxymorphone is maintained to allow the controlled release dosage to be used to treat patients suffering moderate to severe pain with once or twice daily dosing. The dosing form of the present invention can also be used with thrice daily dosing.

It is critical when considering the present invention that the difference between a controlled release tablet and an immediate release formulation be fully understood. In classical terms, an immediate release formulation releases at least 80% of its active pharmaceutical ingredient within 30 minutes. With reference to the present invention, the definition of an immediate release formulation will be broadened further to include a formulation which releases more than about 80% of its active pharmaceutical ingredient within 60 minutes in a standard USP Paddle Method dissolution test at 50 rpm in 500 ml media having a pH of between 1.2 and 6.8 at 37° C. "Controlled release" formulations, as referred to herein, will then encompass any formulations which release no more than about 80% of their active pharmaceutical ingredients within 60 minutes under the same conditions.

The controlled release dosage form of this invention exhibits a dissolution rate in vitro, when measured by USP Paddle Method at 50 rpm in 500 ml media having a pH between 1.2 and 6.8 at 37° C., of about 15% to about 50% by weight oxymorphone released after 1 hour, about 45% to about 80% by weight oxymorphone released after 4 hours, and at least about 80% by weight oxymorphone released after 10 hours.

When administered orally to humans, an effective controlled release dosage form of oxymorphone should exhibit the following in vivo characteristics: (a) peak plasma level of oxymorphone occurs within about 1 to about 8 hours after administration; (b) peak plasma level of 6-OH oxymorphone occurs within about 1 to about 8 hours after administration; (c) duration of analgesic effect is through about 8 to about 24 hours after administration; (d) relative oxymorphone bioavailability is in the range of about 0.5 to about 1.5 compared to an orally-administered aqueous solution of oxymorphone; and (e) the ratio of the area under the curve of blood plasma level vs. time for 6-OH oxymorphone compared to oxymorphone is in the range of about 0.5 to about 1.5. Of course, there is variation of these parameters among subjects, depending on the size and weight of the individual subject, the subject's age, individual metabolism differences, and other factors. Indeed, the parameters may vary in an individual from day to day. Accordingly, the parameters set forth above are intended to be mean values from a sufficiently large study so as to minimize the effect of individual variation in arriving at the values. A convenient method for arriving at such values is by conducting a study in accordance with standard FDA procedures such as those employed in producing results for use in a new drug application (or abbreviated new drug application) before the FDA. Any reference to mean values herein, in conjunction with desired results, refer to results from such a study, or some comparable study. Reference to mean values reported herein for studies actually conducted are arrived at using standard statistical methods as would be employed by one skilled in the art of pharmaceutical formulation and testing for regulatory approval.

In one specific embodiment of the controlled release matrix form of the invention, the oxymorphone or salt of oxymorphone is dispersed in a controlled release delivery system that comprises a hydrophilic material which, upon exposure to gastrointestinal fluid, forms a gel matrix that releases oxymorphone at a controlled rate. The rate of release of oxymorphone from the matrix depends on the drug's partition coefficient between components of the matrix and the aqueous phase within the gastrointestinal tract. In a preferred form of this embodiment, the hydrophilic material of the controlled release delivery system comprises a mixture of a heteropolysaccharide gum and an agent capable of cross-linking the heteropolysaccharide in presence of gastrointestinal fluid. The controlled release delivery system may also comprise a water-soluble pharmaceutical diluent mixed with the hydrophilic material. Preferably, the cross-linking agent is a homopolysaccharide gum and the inert pharmaceutical diluent is a monosaccharide, a disaccharide, or a polyhydric alcohol, or a mixture thereof.

In a specific preferred embodiment, the appropriate blood plasma levels of oxymorphone and 6-hydroxy oxymorphone are achieved using oxymorphone in the form of oxymorphone hydrochloride, wherein the weight ratio of heteropolysaccharide to homopolysaccharide is in the range of about 1:3 to about 3:1, the weight ratio of heteropolysaccharide to diluent is in the range of about 1:8 to about 8:1, and the weight ratio of heteropolysaccharide to oxymorphone hydrochloride is in the range of about 10:1 to about 1:10. A preferred heteropolysaccharide is xanthan gum and a preferred homopolysaccharide is locust bean gum. The dosage form also comprises a cationic cross-linking agent and a hydrophobic polymer. In the preferred embodiment, the dosage form is a tablet containing about 5 mg to about 80 mg of oxymorphone hydrochloride. In a most preferred embodiment, the tablet contains about 20 mg oxymorphone hydrochloride.

The invention includes a method which comprises achieving appropriate blood plasma levels of drug while providing extended pain relief by administering one to three times per day to a patient suffering moderate to severe, acute or chronic pain, an oxymorphone controlled release oral solid dosage form of the invention in an amount sufficient to alleviate the pain for a period of about 8 hours to about 24 hours. This type and intensity of pain is often associated with cancer, autoimmune diseases, infections, surgical and accidental traumas and osteoarthritis.

The invention also includes a method of making an oxymorphone controlled release oral solid dosage form of the invention which comprises mixing particles of oxymorphone or a pharmaceutically acceptable salt of oxymorphone with granules comprising the controlled release delivery system, preferably followed by directly compressing the mixture to form tablets.

Pharmaceutically acceptable salts of oxymorphone which can be used in this invention include salts with the inorganic and organic acids which are commonly used to produce non-toxic salts of medicinal agents. Illustrative examples would be those salts formed by mixing oxymorphone with hydrochloric, sulfuric, nitric, phosphoric, phosphorous, hydrobromic, maleric, malic, ascorbic, citric or tartaric, pamoic, lauric, stearic, palmitic, oleic, myristic, lauryl sulfuric, naphthylenesulfonic, linoleic or linolenic acid, and the like. The hydrochloride salt is preferred.

It has now been found that 6-OH oxymorphone, which is one of the metabolites of oxymorphone, may play a role in alleviating pain. When oxymorphone is ingested, part of the dosage gets into the bloodstream to provide pain relief, while another part is metabolized to 6-OH oxymorphone. This metabolite then enters the bloodstream to provide further pain relief. Thus it is believed that both the oxymorphone and 6-hydroxyoxymorphone levels are important to pain relief.

The effectiveness of oxymorphone and 6-hydroxyoxymorphone at relieving pain and the pharmacokinetics of a single dose of oxymorphone were studied. The blood plasma levels of both oxymorphone and 6-hydroxyoxymorphone were measured in patients after a single dose of oxymorphone was administered. Similarly, the pain levels in patients were measured after a single administration of oxymorphone to determine the effective duration of pain relief from a single dose. FIGS. **1-2** show the results of these tests, comparing pain levels to oxymorphone and 6-hydroxy oxymorphone levels.

For these tests, pain was measured using a Visual Analog Scale (VAS) or a Categorical Scale. The VAS scales consisted of a horizontal line, 100 mm in length. The left-hand end of the scale (0 mm) was marked with the descriptor "No Pain" and the right-hand end of the scale (100 mm) was marked with the descriptor "Extreme Pain". Patients indicated their level of pain by making a vertical mark on the line. The VAS score was equal to the distance (in mm) from the left-hand end of the scale to the patient's mark. For the categorical scale, patients completed the following statement, "My pain at this time is" using the scale None=0, Mild=1, Moderate=2, or Severe=3.

As can be seen from these figures, there is a correlation between pain relief and both oxymorphone and 6-hydroxyoxymorphone levels. As the blood plasma levels of oxymorphone and 6-hydroxyoxymorphone increase, pain decreases (and pain intensity difference and pain relief increases). Thus, to the patient, it is the level of oxymorphone and 6-hydroxyoxymorphone in the blood plasma which is most important. Further it is these levels which dictate the efficacy of the dosage form. A dosage form which maintains a sufficiently high level of oxymorphone or 6-hydroxyoxymorphone for a longer period need not be administered frequently. Such a result is accomplished by embodiments of the present invention.

The oxymorphone controlled release oral solid dosage form of this invention can be made using any of several different techniques for producing controlled release oral solid dosage forms of opioid analgesics.

In one embodiment, a core comprising oxymorphone or oxymorphone salt is coated with a controlled release film which comprises a water insoluble material and which upon exposure to gastrointestinal fluid releases oxymorphone from the core at a controlled rate. In a second embodiment, the oxymorphone or oxymorphone salt is dispersed in a controlled release delivery system that comprises a hydrophilic material which upon exposure to gastrointestinal fluid forms a gel matrix that releases oxymorphone at a controlled rate. A third embodiment is a combination of the first two: a controlled release matrix coated with a controlled release film. In a fourth embodiment the oxymorphone is incorporated into an osmotic pump. In any of these embodiments, the dosage form can be a tablet, a plurality of granules in a capsule, or other suitable form, and can contain lubricants, colorants, diluents, and other conventional ingredients.

Osmotic Pump

An osmotic pump comprises a shell defining an interior compartment and having an outlet passing through the shell. The interior compartment contains the active pharmaceutical ingredient. Generally the active pharmaceutical ingredient is mixed with excipients or other compositions such as a polyalkylene. The shell is generally made, at least in part, from a material (such as cellulose acetate) permeable to the liquid of the environment where the pump will be used, usually stomach acid. Once ingested, the pump operates when liquid diffuses through the shell of the pump. The liquid dissolves the composition to produce a saturated situation. As more liquid diffuses into the pump, the saturated solution containing the pharmaceutical is expelled from the pump through the outlet. This produces a nearly constant release of active ingredient, in the present case, oxymorphone.

Controlled Release Coating

In this embodiment, a core comprising oxymorphone or oxymorphone salt is coated with a controlled release film which comprises a water insoluble material. The film can be applied by spraying an aqueous dispersion of the water insoluble material onto the core. Suitable water insoluble materials include alkyl celluloses, acrylic polymers, waxes (alone or in admixture with fatty alcohols), shellac and zein. The aqueous dispersions of alkyl celluloses and acrylic polymers preferably contain a plasticizer such as triethyl citrate, dibutyl phthalate, propylene glycol, and polyethylene glycol. The film coat can contain a water-soluble material such as polyvinylpyrrolidone (PVP) or hydroxypropylmethylcellulose (HPMC).

The core can be a granule made, for example, by wet granulation of mixed powders of oxymorphone or oxymorphone salt and a binding agent such as HPMC, or by coating an inert bead with oxymorphone or oxymorphone salt and a binding agent such as HPMC, or by spheronising mixed powders of oxymorphone or oxymorphone salt and a spheronising agent such as microcrystalline cellulose. The core can be a tablet made by compressing such granules or by compressing a powder comprising oxymorphone or oxymorphone salt.

The in vitro and in vivo release characteristics of this controlled release dosage form can be modified by using mixtures of different water insoluble and water soluble materials, using different plasticizers, varying the thickness of the controlled release film, including release-modifying agents in the coating, or by providing passageways through the coating.

Controlled Release Matrix

It is important in the present invention that appropriate blood plasma levels of oxymorphone and 6-hydroxy oxymorphone be achieved and maintained for sufficient time to provide pain relief to a patient for a period of 12 to 24 hours. The preferred composition for achieving and maintaining the proper blood plasma levels is a controlled-release matrix. In this embodiment, the oxymorphone or oxymorphone salt is dispersed in a controlled release delivery system that comprises a hydrophilic material (gelling agent) which upon exposure to gastrointestinal fluid forms a gel matrix that releases oxymorphone at a controlled rate. Such hydrophilic materials include gums, cellulose ethers, acrylic resins, and protein-derived materials. Suitable cellulose ethers include hydroxyalkyl celluloses and carboxyalkyl celluloses, especially hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), HPMC, and carboxy methylcellulose (CMC). Suitable acrylic resins include polymers and copolymers of acrylic acid, methacrylic acid, methyl acrylate and methyl methacrylate. Suitable gums include heteropolysaccharide and homopolysaccharide gums, e.g., xanthan, tragacanth, acacia, karaya, alginates, agar, guar, hydroxypropyl guar, carrageenan, and locust bean gums.

Preferably, the controlled release tablet of the present invention is formed from (I) a hydrophilic material comprising (a) a heteropolysaccharide; or (b) a heteropolysaccharide

and a cross-linking agent capable of cross-linking said heteropolysaccharide; or (c) a mixture of (a), (b) and a polysaccharide gum; and (II) an inert pharmaceutical filler comprising up to about 80% by weight of the tablet; and (III) oxymorphone.

The term "heteropolysaccharide" as used herein is defined as a water-soluble polysaccharide containing two or more kinds of sugar units, the heteropolysaccharide having a branched or helical configuration, and having excellent water-wicking properties and immense thickening properties.

A preferred heteropolysaccharide is xanthan gum, which is a high molecular weight (>10^6) heteropolysaccharide. Other preferred heteropolysaccharides include derivatives of xanthan gum, such as deacylated xanthan gum, the carboxymethyl ether, and the propylene glycol ester.

The cross linking agents used in the controlled release embodiment of the present invention which are capable of cross-linking with the heteropolysaccharide include homopolysaccharide gums such as the galactomannans, i.e., polysaccharides which are composed solely of mannose and galactose. Galactomannans which have higher proportions of unsubstituted mannose regions have been found to achieve more interaction with the heteropolysaccharide. Locust bean gum, which has a higher ratio of mannose to the galactose, is especially preferred as compared to other galactomannans such as guar and hydroxypropyl guar.

Preferably, the ratio of heteropolysaccharide to homopolysaccharide is in the range of about 1:9 to about 9:1, preferably about 1:3 to about 3:1. Most preferably, the ratio of xanthan gum to polysaccharide material (i.e., locust bean gum, etc.) is preferably about 1:1.

In addition to the hydrophilic material, the controlled release delivery system can also contain an inert pharmaceutical diluent such as a monosaccharide, a disaccharide, a polyhydric alcohol and mixtures thereof. The ratio of diluent to hydrophilic matrix-forming material is generally in the range of about 1:3 to about 3:1.

The controlled release properties of the controlled release embodiment of the present invention may be optimized when the ratio of heteropolysaccharide gum to homopolysaccharide material is about 1:1, although heteropolysaccharide gum in an amount of from about 20 to about 80% or more by weight of the heterodisperse polysaccharide material provides an acceptable slow release product. The combination of any homopolysaccharide gums known to produce a synergistic effect when exposed to aqueous solutions may be used in accordance with the present invention. It is also possible that the type of synergism which is present with regard to the gum combination of the present invention could also occur between two homogeneous or two heteropolysaccharides. Other acceptable gelling agents which may be used in the present invention include those gelling agents well-known in the art. Examples include vegetable gums such as alginates, carrageenan, pectin, guar gum, xanthan gum, modified starch, hydroxypropylmethylcellulose, methylcellulose, and other cellulosic materials such as sodium carboxymethylcellulose and hydroxypropyl cellulose. This list is not meant to be exclusive.

The combination of xanthan gum with locust bean gum with or without the other homopolysaccharide gums is an especially preferred gelling agent. The chemistry of certain of the ingredients comprising the excipients of the present invention such as xanthan gum is such that the excipients are considered to be self-buffering agents which are substantially insensitive to the solubility of the medicament and likewise insensitive to the pH changes along the length of the gastrointestinal tract.

The inert filler of the sustained release excipient preferably comprises a pharmaceutically acceptable saccharide, including a monosaccharide, a disaccharide, or a polyhydric alcohol, and/or mixtures of any of the foregoing. Examples of suitable inert pharmaceutical fillers include sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol, sorbitol, mixtures thereof and the like. However, it is preferred that a soluble pharmaceutical filler such as lactose, dextrose, sucrose, or mixtures thereof be used.

The cationic cross-linking agent which is optionally used in conjunction with the controlled release embodiment of the present invention may be monovalent or multivalent metal cations. The preferred salts are the inorganic salts, including various alkali metal and/or alkaline earth metal sulfates, chlorides, borates, bromides, citrates, acetates, lactates, etc. Specific examples of suitable cationic cross-linking agents include calcium sulfate, sodium chloride, potassium sulfate, sodium carbonate, lithium chloride, tripotassium phosphate, sodium borate, potassium bromide, potassium fluoride, sodium bicarbonate, calcium chloride, magnesium chloride, sodium citrate, sodium acetate, calcium lactate, magnesium sulfate and sodium fluoride. Multivalent metal cations may also be utilized. However, the preferred cationic cross-linking agents are bivalent. Particularly preferred salts are calcium sulfate and sodium chloride. The cationic cross-linking agents of the present invention are added in an amount effective to obtain a desirable increased gel strength due to the cross-linking of the gelling agent (e.g., the heteropolysaccharide and homopolysaccharide gums). In preferred embodiments, the cationic cross-linking agent is included in the sustained release excipient of the present invention in an amount from about 1 to about 20% by weight of the sustained release excipient, and in an amount about 0.5% to about 16% by weight of the final dosage form.

In the controlled release embodiments of the present invention, the sustained release excipient comprises from about 10 to about 99% by weight of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum, from about 1 to about 20% by weight of a cationic crosslinking agent, and from about 0 to about 89% by weight of an inert pharmaceutical diluent. In other embodiments, the sustained release excipient comprises from about 10 to about 75% gelling agent, from about 2 to about 15% cationic crosslinking agent, and from about 30 to about 75% inert diluent. In yet other embodiments, the sustained release excipient comprises from about 30 to about 75% gelling agent, from about 5 to about 10% cationic cross-linking agent, and from about 15 to about 65% inert diluent.

The sustained release excipient used in this embodiment of the present invention (with or without the optional cationic cross-linking agent) may be further modified by incorporation of a hydrophobic material which slows the hydration of the gums without disrupting the hydrophilic matrix. This is accomplished in preferred embodiments of the present invention by granulating the sustained release excipient with the solution or dispersion of a hydrophobic material prior to the incorporation of the medicament. The hydrophobic polymer may be selected from an alkylcellulose such as ethylcellulose, other hydrophobic cellulosic materials, polymers or copolymers derived from acrylic or methacrylic acid esters, copolymers of acrylic and methacrylic acid esters, zein, waxes, shellac, hydrogenated vegetable oils, and any other pharmaceutically acceptable hydrophobic material known to those skilled in the art. The amount of hydrophobic material incor-

porated into the sustained release excipient is that which is effective to slow the hydration of the gums without disrupting the hydrophilic matrix formed upon exposure to an environmental fluid. In certain preferred embodiments of the present invention, the hydrophobic material is included in the sustained release excipient in an amount from about 1 to about 20% by weight. The solvent for the hydrophobic material may be an aqueous or organic solvent, or mixtures thereof.

Examples of commercially available alkylcelluloses are Aquacoat coating (aqueous dispersion of ethylcellulose available from FMC of Philadelphia, Pa.) and Surelease coating (aqueous dispersion of ethylcellulose available from Colorcon of West Point, Pa.). Examples of commercially available acrylic polymers suitable for use as the hydrophobic material include Eudragit RS and RL polymers (copolymers of acrylic and methacrylic acid esters having a low content (e.g., 1:20 or 1:40) of quaternary ammonium compounds available from Rohm America of Piscataway, N.J.).

The controlled release matrix useful in the present invention may also contain a cationic cross-linking agent such as calcium sulfate in an amount sufficient to cross-link the gelling agent and increase the gel strength, and an inert hydrophobic material such as ethyl cellulose in an amount sufficient to slow the hydration of the hydrophilic material without disrupting it. Preferably, the controlled release delivery system is prepared as a pre-manufactured granulation.

EXAMPLES

Example 1

Two controlled release delivery systems are prepared by dry blending xanthan gum, locust bean gum, calcium sulfate dehydrate, and dextrose in a high speed mixed/granulator for 3 minutes. A slurry is prepared by mixing ethyl cellulose with alcohol. While running choppers/impellers, the slurry is added to the dry blended mixture, and granulated for another 3 minutes. The granulation is then dried to a LOD (loss on drying) of less than about 10% by weight. The granulation is then milled using 20 mesh screen. The relative quantities of the ingredients are listed in the table below.

TABLE 1

Controlled Release Delivery System

Excipient	Formulation 1 (%)	Formulation 2 (%)
Locust Bean Gum, FCC	25.0	30.0
Xanthan Gum, NF	25.0	30.0
Dextrose, USP	35.0	40.0
Calcium Sulfate Dihydrate, NF	10.0	0.0
Ethylcellulose, NF	5.0	0.0
Alcohol, SD3A (Anhydrous)	(10)[1]	(20.0)[1]
Total	100.0	100.0

A series of tablets containing different amounts of oxymorphone hydrochloride were prepared using the controlled release delivery Formulation 1 shown in Table 1. The quantities of ingredients per tablet are as listed in the following table.

TABLE 2

Sample Tablets of Differing Strengths

Component	Amounts in Tablet (mg)				
Oxymorphone HCl, USP (mg)*	5	10	20	40	80
Controlled release delivery system	160	160	160	160	160
Silicified microcrystalline cellulose, N.F.	20	20	20	20	20
Sodium stearyl fumarate, NF	2	2	2	2	2
Total weight	187	192	202	222	262
Opadry (colored)	7.48	7.68	8.08	8.88	10.48
Opadry (clear)	0.94	0.96	1.01	1.11	1.31

Examples 2 and 3

Two batches of 20 mg tablets were prepared as described above, using the controlled release delivery system of Formulation 1. One batch was formulated to provide relatively fast controlled release, the other batch was formulated to provide relatively slow controlled release. Compositions of the tablets are shown in the following table.

TABLE 3

Slow and Fast Release Compositions

Ingredients	Example 2 Slow (mg)	Example 3 Fast (mg)	Example 4 Fast (mg)
Oxymorphone HCl, USP	20	20	20
Controlled Release Delivery System	360	160	160
Silicified Microcrystalline Cellulose, NF	20	20	20
Sodium stearyl fumarate, NF	4	2	2
Total weight	404	202	202
Coating (color or clear)	12	12	9

The tablets of Examples 2, 3, and 4 were tested for in vitro release rate according to USP Procedure Drug Release U.S. Pat. No. 23. Release rate is a critical variable in attempting to control the blood plasma levels of oxymorphone and 6-hydroxyoxymorphone in a patient. Results are shown in the following Table 4.

TABLE 4

Release Rates of Slow and Fast Release Tablets

Time (hr)	Example 2 (Slow Release)	Example 3 (Fast Release)	Example 4 (Fast Release)
0.5	18.8	21.3	20.1
1	27.8	32.3	31.7
2	40.5	47.4	46.9
3	50.2	58.5	57.9
4	58.1	66.9	66.3
5	64.7	73.5	74.0
6	70.2	78.6	83.1
8	79.0	86.0	92.0
10	85.3	90.6	95.8
12	89.8	93.4	97.3

Clinical Studies

Three clinical studies were conducted to assess the bioavailability (rate and extent of absorption) of oxymorphone. Study 1 addressed the relative rates of absorption of con-

trolled release (CR) oxymorphone tablets (of Examples 2 and 3) and oral oxymorphone solution in fasted patients. Study 2 addressed the relative rates of absorption of CR oxymorphone tablets (of Examples 2 and 3) and oral oxymorphone solution in fed patients. Study 3 addressed the relative rates of absorption of CR oxymorphone tablets (of Example 4) and oral oxymorphone solution in fed and fasted patients.

The blood plasma levels set forth herein as appropriate to achieve the objects of the present invention are mean blood plasma levels. As an example, if the blood plasma level of oxymorphone in a patient 12 hours after administration of a tablet is said to be at least 0.5 ng/ml, any particular individual may have lower blood plasma levels after 12 hours. However, the mean minimum concentration should meet the limitation set forth. To determine mean parameters, a study should be performed with a minimum of 8 adult subjects, in a manner acceptable for filing an application for drug approval with the US Food and Drug Administration. In cases where large fluctuations are found among patients, further testing may be necessary to accurately determine mean values.

For all studies, the following procedures were followed, unless otherwise specified for a particular study.

The subjects were not to consume any alcohol-, caffeine-, or xanthine-containing foods or beverages for 24 hours prior to receiving study medication for each study period. Subjects were to be nicotine and tobacco free for at least 6 months prior to enrolling in the study. In addition, over-the-counter medications were prohibited 7 days prior to dosing and during the study. Prescription medications were not allowed 14 days prior to dosing and during the study.

Pharmacokinetic and Statistical Methods

The following pharmacokinetic parameters were computed from the plasma oxymorphone concentration-time data:

$AUC_{(0-t)}$ Area under the drug concentration-time curve from time zero to the time of the last quantifiable concentration (Ct), calculated using linear trapezoidal summation.

$AUC_{(0-inf)}$ Area under the drug concentration-time curve from time zero to infinity. $AUC_{(0-inf)}=AUC_{(0-t)}+Ct/K_{el}$, where K_{el} is the terminal elimination rate constant.

$AUC_{(0-24)}$ Partial area under the drug concentration-time curve from time zero to 24 hours.

C_{max} Maximum observed drug concentration.

T_{max} Time of the observed maximum drug concentration.

K_{el} Elimination rate constant based on the linear regression of the terminal linear portion of the LN (concentration) time curve.

Terminal elimination rate constants for use in the above calculations were in turn computed using linear regression of a minimum of three time points, at least two of which were consecutive. K_{el} values for which correlation coefficients were less than or equal to 0.8 were not reported in the pharmacokinetic parameter tables or included in the statistical analysis. Thus $AUC_{(0-inf)}$ was also not reported in these cases.

A parametric (normal-theory) general linear model was applied to each of the above parameters (excluding T_{max}), and the LN-transformed parameters C_{max}, $AUC_{(0-24)}$, $AUC_{(0-t)}$, and $AUC_{(0-inf)}$. Initially, the analysis of variance (ANOVA) model included the following factors: treatment, sequence, subject within sequence, period, and carryover effect. If carryover effect was not significant, it was dropped from the model. The sequence effect was tested using the subject within sequence mean square, and all other main effects were tested using the residual error (error mean square).

Plasma oxymorphone concentrations were listed by subject at each collection time and summarized using descriptive statistics. Pharmacokinetic parameters were also listed by subject and summarized using descriptive statistics.

Study 1-Two Controlled Release Formulations; Fasted Patients

Healthy volunteers received a single oral dose of 20 mg CR oxymorphone taken with 240 ml water after a 10-hour fast. Subjects received the tablets of Example 2 (Treatment 1A) or Example 3 (Treatment 1B). Further subjects were given a single oral dose of 10 mg/10 ml oxymorphone solution in 180 ml apple juice followed with 60 ml water (Treatment 1C). The orally dosed solution was used to simulate an immediate release (IR) dose.

This study had a single-center, open-label, randomized, three-way crossover design using fifteen subjects. Subjects were in a fasted state following a 10-hour overnight fast. There was a 14-day washout interval between the three dose administrations. The subjects were confined to the clinic during each study period. Subjects receiving Treatment 1C were confined for 18 hours and subjects receiving Treatments 1A or 1B were confined for 48 hours after dosing. Ten-milliliter blood samples were collected during each study period at the 0 hour (predose), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, and 48 hours postdose for subjects receiving Treatment 1A or 1B and 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 18 hours post-dose. The mean plasma concentration of oxymorphone versus time for each treatment across all subjects is shown in table 5.

TABLE 5

Mean Plasma Concentration vs. Time (ng/ml)

Time (hr)	Treatment 1A	Treatment 1B	Treatment 1C
0	0.000	0.000	0.0000
0.25			0.9489
0.5	0.2941	0.4104	1.3016
0.75			1.3264
1	0.5016	0.7334	1.3046
1.25			1.2041
1.5	0.5951	0.8192	1.0813
1.75			0.9502
2	0.6328	0.7689	0.9055
2.5			0.7161
3	0.5743	0.7341	0.6689
4	0.5709	0.6647	0.4879
5	0.7656	0.9089	0.4184
6	0.7149	0.7782	0.3658
7	0.6334	0.6748	0.3464
8	0.5716	0.5890	0.2610
10	0.4834	0.5144	0.2028
12	0.7333	0.6801	0.2936
14	0.6271	0.6089	0.2083
16	0.4986	0.4567	0.1661
18	0.4008	0.3674	0.1368
20	0.3405	0.2970	
24	0.2736	0.2270	
28	0.3209	0.2805	
32	0.2846	0.2272	
36	0.2583	0.1903	
48	0.0975	0.0792	

The results are shown graphically in FIG. 5. In both Table 5 and FIG. 5, the results are normalized to a 20 mg dosage. The immediate release liquid of Treatment 1C shows a classical curve, with a high and relatively narrow peak, followed by an exponential drop in plasma concentration. However, the controlled release oxymorphone tablets exhibit triple peaks in blood plasma concentration. The first peak occurs (on average) at around 3 hours. The second peak of the mean blood plasma concentration is higher than the first, occurring around 6-7 hours, on average).

Occasionally, in an individual, the first peak is higher than the second, although generally this is not the case. This makes it difficult to determine the time to maximum blood plasma concentration (T_{max}) because if the first peak is higher than the second, maximum blood plasma concentration (C_{max}) occurs much earlier (at around 3 hours) than in the usual case where the second peak is highest. Therefore, when we refer to the time to peak plasma concentration (T_{max}) unless otherwise specified, we refer to the time to the second peak. Further, when reference is made to the second peak, we refer to the time or blood plasma concentration at the point where the blood plasma concentration begins to drop the second time. Generally, where the first peak is higher than the second, the difference in the maximum blood plasma concentration at the two peaks is small. Therefore, this difference (if any) was ignored and the reported C_{max} was the true maximum blood plasma concentration and not the concentration at the second peak.

TABLE 6

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 1

	Treatment 1A		Treatment 1B		Treatment 1C	
	Mean	SD	Mean	SD	Mean	SD
C_{max}	0.8956	0.2983	1.0362	0.3080	2.9622	1.0999
T_{max}	7.03	4.10	4.89	3.44	0.928	0.398
$AUC_{(0-t)}$	17.87	6.140	17.16	6.395	14.24	5.003
$AUC_{(0-inf)}$	19.87	6.382	18.96	6.908	16.99	5.830
$T_{1/2el}$	10.9	2.68	11.4	2.88	6.96	4.61

Units:
C_{max} in ng/ml,
T_{max} in hours,
AUC in ng * hr/ml,
$T_{1/2el}$ in hours.

Relative bioavailability determinations are set forth in Tables 7 and 8. For these calculations, AUC was normalized for all treatments to a 20 mg dose.

TABLE 7

Relative Bioavailability (F_{rel}) Determination Based on $AUC_{(0-inf)}$

F_{rel} (1A vs. 1C)	F_{rel} (1B vs. 1C)	F_{rel} (1A vs. 1B)
1.193 .±. 0.203	1.121 .±. 0.211	1.108 .±. 0.152

TABLE 8

Relative Bioavailability Determination Based on $AUC_{(0-18)}$

F_{rel} (1A vs. 1C)	F_{rel} (1B vs. 1C)	F_{rel} (1A vs. 1B)
0.733 .±. 0.098	0.783 .±. 0.117	0.944 .±. 0.110

Study 2-Two CR Formulations; Fed Patients

Healthy volunteers received a single oral dose of 20 mg CR oxymorphone taken with 240 ml water in a fed state. Subjects received the tablets of Example 2 (Treatment 2A) or Example 3 (Treatment 2B). Further subjects were given a single oral dose of 10 mg/10 ml oxymorphone solution in 180 ml apple juice followed with 60 ml water (Treatment 2C). The orally dosed solution was used to simulate an immediate release (IR) dose.

This study had a single-center, open-label, randomized, three-way crossover design using fifteen subjects. The subjects were in a fed state, after a 10-hour overnight fast followed by a standardized FDA high-fat breakfast. There was a 14-day washout interval between the three dose administrations. The subjects were confined to the clinic during each study period. Subjects receiving Treatment 2C were confined for 18 hours and subjects receiving Treatments 2A or 2B were confined for 48 hours after dosing. Ten-milliliter blood samples were collected during each study period at the 0 hour (predose), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, and 48 hours postdose for subjects receiving Treatment 2A or 2B and 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 18 hours postdose. The mean plasma concentration of oxymorphone versus time for each treatment across all subjects is shown in table 9.

TABLE 9

Mean Plasma Concentration vs. Time (ng/ml)

Time (hr)	Treatment 2A	Treatment 2B	Treatment 2C
0	0.000	0.000	0.0000
0.25			1.263
0.5	0.396	.0553	1.556
0.75			1.972
1	0.800	1.063	1.796
1.25			1.795
1.5	1.038	1.319	1.637
1.75			1.467
2	1.269	1.414	1.454
2.5			1.331
3	1.328	1.540	1.320
4	1.132	1.378	1.011
5	1.291	1.609	0.731
6	1.033	1.242	0.518
7	0.941	0.955	0.442
8	0.936	0.817	0.372
10	0.669	0.555	0.323
12	0.766	0.592	0.398
14	0.641	0.519	0.284
16	0.547	0.407	0.223
18	0.453	0.320	0.173
20	0.382	0.280	
24	0.315	0.254	
28	0.352	0.319	
32	0.304	0.237	
36	0.252	0.207	
48	0.104	0.077	

The results are shown graphically in FIG. 6. Again, the results have been normalized to a 20 mg dosage. As with Study 1, the immediate release liquid of Treatment 2C shows a classical curve, with a high and relatively narrow peak, followed by an exponential drop in plasma concentration, while the controlled release oxymorphone tablets exhibit triple peaks in blood plasma concentration. Thus, again when we refer to the time to peak plasma concentration (T_{max}) unless otherwise specified, we refer to the time to the second peak.

TABLE 10

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 2

	Treatment 2A		Treatment 2B		Treatment 2C	
	Mean	SD	Mean	SD	Mean	SD
C_{max}	1.644	0.365	1.944	0.465	4.134	0.897
T_{max}	3.07	1.58	2.93	1.64	0.947	0.313
$AUC_{(0-t)}$	22.89	5.486	21.34	5.528	21.93	5.044

TABLE 10-continued

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 2

	Treatment 2A		Treatment 2B		Treatment 2C	
	Mean	SD	Mean	SD	Mean	SD
$AUC_{(0\text{-}inf)}$	25.28	5.736	23.62	5.202	24.73	6.616
$T_{1/2el}$	12.8	3.87	11.0	3.51	5.01	2.02

Units:
C_{max} in ng/ml,
T_{max} in hours,
AUC in ng * hr/ml,
$T_{1/2el}$ in hours.

In Table 10, the T_{max} has a large standard deviation due to the two comparable peaks in blood plasma concentration. Relative bioavailability determinations are set forth in Tables 11 and 12.

TABLE 11

Relative Bioavailability Determination Based on $AUC_{(0\text{-}inf)}$

F_{rel} (2A vs. 2C)	F_{rel} (2B vs. 2C)	F_{rel} (2A vs. 2B)
1.052 .±. 0.187	0.949 .±. 0.154	1.148 .±. 0.250

TABLE 12

Relative bioavailability Determination Based on $AUC_{(0\text{-}18)}$

F_{rel} (2A vs. 2C)	F_{rel} (2B vs. 2C)	F_{rel} (2A vs. 2B)
0.690 .±. 0.105	0.694 .±. 0.124	1.012 .±. 0.175

As may be seen from tables 5 and 10 and FIGS. 1 and 2, the C_{max} for the CR tablets (treatments 1A, 1B, 2A and 2B) is considerably lower, and the T_{max} much higher than for the immediate release oxymorphone. The blood plasma level of oxymorphone remains high well past the 8 (or even the 12) hour dosing interval desired for an effective controlled release tablet.

Study 3-One Controlled Release Formulation; Fed and Fasted Patients

This study had a single-center, open-label, analytically blinded, randomized, four-way crossover design. Subjects randomized to Treatment 3A and Treatment 3C, as described below, were in a fasted state following a 10-hour overnight fast. Subjects randomized to Treatment 3B and Treatment 3D, as described below, were in the fed state, having had a high fat meal, completed ten minutes prior to dosing. There was a 14-day washout interval between the four dose administrations. The subjects were confined to the clinic during each study period. Subjects assigned to receive Treatment 3A and Treatment 3B were discharged from the clinic on Day 3 following the 48-hour procedures, and subjects assigned to receive Treatment 3C and Treatment 3D were discharged from the clinic on Day 2 following the 36-hour procedures. On Day 1 of each study period the subjects received one of four treatments:

Treatments 3A and 3B: Oxymorphone controlled release 20 mg tablets from Example 3. Subjects randomized to Treatment 3A received a single oral dose of one 20 mg oxymorphone controlled release tablet taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 3B received a single oral dose of one 20 mg oxymorphone controlled release tablet taken with 240 ml of water 10 minutes after a standardized high fat meal.

Treatments 3C and 3D: oxymorphone HCl solution, USP, 1.5 mg/ml 10 ml vials. Subjects randomized to Treatment 3C received a single oral dose of 10 mg (6.7 ml) oxymorphone solution taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 3D received a single oral dose of 10 mg (6.7 ml) oxymorphone solution taken with 240 ml of water 10 minutes after a standardized high-fat meal.

A total of 28 male subjects were enrolled in the study, and 24 subjects completed the study. The mean age of the subjects was 27 years (range of 19 through 38 years), the mean height of the subjects was 69.6 inches (range of 64.0 through 75.0 inches), and the mean weight of the subjects was 169.0 pounds (range 117.0 through 202.0 pounds).

A total of 28 subjects received at least one treatment. Only subjects who completed all 4 treatments were included in the summary statistics and statistical analysis.

Blood samples (7 ml) were collected during each study period at the 0 hour (predose), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, 24, 30, 36, and 48 hours post-dose (19 samples) for subjects randomized to Treatment 3A and Treatment 3B. Blood samples (7 ml) were collected during each study period at the 0 hour (predose), and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, and 36 hours post-dose (21 samples) for subjects randomized to Treatment 3C and Treatment 3D.

The mean oxymorphone plasma concentration versus time curves for Treatments 3A, 3B, 3C, and 3D are presented in FIG. 7. The results have been normalized to a 20 mg dosage. The data is contained in Table 13. The arithmetic means of the plasma oxymorphone pharmacokinetic parameters and the statistics for all Treatments are summarized in Table 14.

TABLE 13

Mean Plasma Concentration vs. Time (ng/ml)

Time (hr)	Treatment 3A	Treatment 3B	Treatment 3C	Treatment 3D
0	0.0084	0.0309	0.0558	0.0000
0.25			0.5074	0.9905
0.5	0.3853	0.3380	0.9634	1.0392
0.75			0.9753	1.3089
1	0.7710	0.7428	0.8777	1.3150
1.25			0.8171	1.2274
1.5	0.7931	1.0558	0.7109	1.1638
1.75			0.6357	1.0428
2	0.7370	1.0591	0.5851	0.9424
3	0.6879	0.9858	0.4991	0.7924
4	0.6491	0.9171	0.3830	0.7277
5	0.9312	1.4633	0.3111	0.6512
6	0.7613	1.0441	0.2650	0.4625
8	0.5259	0.7228	0.2038	0.2895
10	0.4161	0.5934	0.1768	0.2470
12	0.5212	0.5320	0.2275	0.2660
14	0.4527	0.4562	0.2081	0.2093
16	0.3924	0.3712	0.1747	0.1623
20	0.2736	0.3021	0.1246	0.1144
24	0.2966	0.2636	0.1022	0.1065
30	0.3460	0.3231		
36	0.2728	0.2456	0.0841	0.0743
48	0.1263	0.1241		

TABLE 14

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 3

	Treatment 3B		Treatment 3A		Treatment 3C		Treatment 3D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max}	1.7895	0.6531	1.1410	0.4537	2.2635	1.0008	3.2733	1.3169
T_{max}	5.65	9.39	5.57	7.14	0.978	1.14	1.11	0.768
$AUC_{(0-24)}$	14.27	4.976	11.64	3.869	12.39	4.116	17.30	5.259
$AUC_{(0-t)}$	19.89	6.408	17.71	8.471	14.53	4.909	19.20	6.030
$AUC_{(0-inf)}$	21.29	6.559	19.29	5.028	18.70	6.618	25.86	10.03
$T_{1/2el}$	12.0	3.64	12.3	3.99	16.2	11.4	20.6	19.3

The relative bioavailability calculations are summarized in tables 15 and 16.

TABLE 15

Relative Bioavailability Determination Based on $AUC_{(0-inf)}$

F_{rel} (3A vs. 3C)	F_{rel} (3B vs. 3D)	F_{rel} (3D vs. 3C)	F_{rel} (3A vs. 3B)
1.040 .±. 0.1874	0.8863 .±. 0.2569	1.368 .±. 0.4328	1.169 .±. 0.2041

TABLE 16

Relative bioavailability Determination Based on $AUC_{(0-24)}$

F_{rel} (3A vs. 2C)	F_{rel} (3B vs. 3D)	F_{rel} (3D vs. 3C)	F_{rel} (3A vs. 3B)
0.9598 .±. 0.2151	0.8344 .±. 0.100	1.470 .±. 0.3922	1.299 .±. 0.4638

The objectives of this study were to assess the relative bioavailability of oxymorphone from oxymorphone controlled release (20 mg) compared to oxymorphone oral solution (10 mg) under both fasted and fed conditions, and to determine the effect of food on the bioavailability of oxymorphone from the controlled release formulation, oxymorphone CR, and from the oral solution.

The presence of a high fat meal had a substantial effect on the oxymorphone C_{max}, but less of an effect on oxymorphone AUC from oxymorphone controlled release tablets. Least Squares (LS) mean C_{max} was 58% higher and LS mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were 18% higher for the fed condition (Treatment B) compared to the fasted condition (Treatment A) based on LN-transformed data. This was consistent with the relative bioavailability determination from $AUC_{(0-inf)}$ since mean F_{rel} was 1.17. Mean T_{max} values were similar (approximately 5.6 hours), and no significant difference in T_{max} was shown using nonparametric analysis. Half value durations were significantly different between the two treatments.

The effect of food on oxymorphone bioavailability from the oral solution was more pronounced, particularly in terms of AUC. LS mean C_{max} was 50% higher and LS mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were 32-34% higher for the fed condition (Treatment D) compared to the fasted condition (Treatment C) based on LN-transformed data. This was consistent with the relative bioavailability determination from $AUC_{(0-inf)}$ since mean F_{rel} was 1.37. Mean T_{max} (approximately 1 hour) was similar for the two treatments and no significant difference was shown.

Under fasted conditions, oxymorphone controlled release 20 mg tablets exhibited similar extent of oxymorphone availability compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment A versus Treatment C). From LN-transformed data, LS mean $AUC_{(0-t)}$ was 17% higher for oxymorphone CR, whereas LS mean $AUC_{(0-inf)}$ values were nearly equal (mean ratio=99%). Mean F_{rel} values calculated from $AUC_{(0-inf)}$ and $AUC_{(0-24)}$, (1.0 and 0.96, respectively) also showed similar extent of oxymorphone availability between the two treatments.

As expected, there were differences in parameters reflecting rate of absorption. LS mean C_{max} was 49% lower for oxymorphone controlled release tablets compared to the dose-normalized oral solution, based on LN-transformed data. Half-value duration was significantly longer for the controlled release formulation (means, 12 hours versus 2.5 hours).

Under fed conditions, oxymorphone availability from oxymorphone controlled release 20 mg was similar compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment B versus Treatment D). From LN-transformed data, LS mean $AUC_{(0-inf)}$ was 12% lower for oxymorphone CR. Mean F_{rel} values calculated from $AUC_{(0-inf)}$ and $AUC_{(0-24)}$, (0.89 and 0.83 respectively) also showed similar extent of oxymorphone availability from the tablet. As expected, there were differences in parameters reflecting rate of absorption. LS mean C_{max} was 46% lower for oxymorphone controlled release tablets compared to the dose-normalized oral solution, based on LN-transformed data. Mean T_{max} was 5.7 hours for the tablet compared to 1.1 hours for the oral solution. Half-value duration was significantly longer for the controlled release formulation (means, 7.8 hours versus 3.1 hours).

The presence of a high fat meal did not appear to substantially affect the availability of 6-hydroxymorphone following administration of oxymorphone controlled release tablets. LS mean ratios were 97% for $AUC_{(0-t)}$ and 91% for C_{max} (Treatment B versus A), based on LN-transformed data. This was consistent with the relative bioavailability determination from $AUC_{(0-24)}$, since mean F_{rel} was 0.97. Mean T_{max}, was

later for the fed treatment compared to the fasted treatment (5.2 and 3.6 hours, respectively), and difference was significant.

Under fasted conditions, oxymorphone controlled release 20 mg tablets exhibited similar availability of 6-hydroxymorphone compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment A versus Treatment C). From LN-transformed data, LS mean ratio for $AUC_{(0-t)}$ was 104.5%. Mean F_{rel} (0.83) calculated from $AUC_{(0-24)}$ also showed similar extent of oxymorphone availability between the two treatments. Mean T_{max} was 3.6 hours for the tablet compared to 0.88 for the oral solution. Half-value duration was significantly longer for the controlled release formulation (means, 11 hours versus 2.2 hours).

Under fed conditions, availability of 6-hydroxymorphone from oxymorphone controlled release 20 mg was similar compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment B versus Treatment D). From LN-transformed data, LS mean $AUC_{(0-t)}$ was 14% higher for oxymorphone CR. Mean F_{rel} (0.87) calculated from $AUC_{(0-24)}$ also indicated similar extent of availability between the treatments. Mean T_{max} was 5.2 hours for the tablet compared to 1.3 hour for the oral solution. Half-value duration was significantly longer for the controlled release formulation (means, 14 hours versus 3.9 hours).

The extent of oxymorphone availability from oxymorphone controlled release 20 mg tablets was similar under fed and fasted conditions since there was less than a 20% difference in LS mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ values for each treatment, based on LN-transformed data. T_{max} was unaffected by food; however, LS mean C_{max} was increased 58% in the presence of the high fat meal. Both rate and extent of oxymorphone absorption from the oxymorphone oral solution were affected by food since LS mean C_{max} and AUC values were increased approximately 50 and 30%, respectively. T_{max} was unaffected by food. Under both fed and fasted conditions, oxymorphone controlled release tablets exhibited similar extent of oxymorphone availability compared to oxymorphone oral solution since there was less than a 20% difference in LS mean AUC(0-t) and AUC(0-inf) values for each treatment.

Bioavailability of 6-hydroxymorphone following oxymorphone controlled release 20 mg tablets was also similar under fed and fasted conditions since there was less than a 20% difference in LS mean C_{max} and AUC values for each treatment. T_{max} was later for the fed condition. The presence of food did not affect the extent of availability from oxymorphone oral solution since LS mean AUC values were less than 20% different. However, C_{max} was decreased 35% in the presence of food. T_{max} was unaffected by food. Under both fed and fasted conditions, oxymorphone controlled release tablets exhibited similar extent of availability compared to oxymorphone oral solution since there was less than a 20% difference in LS mean AUC values for each treatment.

The mean 6-OH oxymorphone plasma concentration versus time curves for Treatments 3A, 3B, 3C, and 3D are presented in FIG. 8. The data is contained in Table 17.

TABLE 17

Mean Plasma Concentration vs. Time (ng/ml) 6-Hydroxyoxymorphone

Time (hr)	Treatment 3A	Treatment 3B	Treatment 3C	Treatment 3D
0	0.0069	0.0125	0.0741	0.0000
0.25			0.7258	0.4918
0.5	0.5080	0.1879	1.2933	0.5972
0.75			1.3217	0.7877
1	1.0233	0.4830	1.1072	0.8080
1.25			1.0069	0.7266
1.5	1.1062	0.7456	0.8494	0.7001
1.75			0.7511	0.6472
2	1.0351	0.7898	0.6554	0.5758
3	0.9143	0.7619	0.6196	0.5319
4	0.8522	0.7607	0.4822	0.5013
5	0.8848	0.8548	0.3875	0.4448
6	0.7101	0.7006	0.3160	0.3451
8	0.5421	0.5681	0.2525	0.2616
10	0.4770	0.5262	0.2361	0.2600
12	0.4509	0.4454	0.2329	0.2431
14	0.4190	0.4399	0.2411	0.2113
16	0.4321	0.4230	0.2385	0.2086
20	0.3956	0.4240	0.2234	0.1984
24	0.4526	0.4482	0.2210	0.2135
30	0.4499	0.4708		
36	0.3587	0.3697	0.1834	0.1672
48	0.3023	0.3279		

TABLE 18

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 3

	Treatment 3A		Treatment 3B		Treatment 3C		Treatment 3D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max}	1.2687	0.5792	1.1559	0.4848	1.5139	0.7616	0.9748	0.5160
T_{max}	3.61	7.17	5.20	9.52	0.880	0.738	1.30	1.04
$AUC_{(0-t)}$	22.47	10.16	22.01	10.77	10.52	4.117	9.550	4.281
$AUC_{(0-inf)}$	38.39	23.02	42.37	31.57	20.50	7.988	23.84	11.37
$T_{1/2el}$	39.1	36.9	39.8	32.6	29.3	12.0	44.0	35.00

Study 4-Controlled Release 20 mg vs Immediate Release 10 mg

A study was conducted to compare the bioavailability and pharmacokinetics of controlled release and immediate release oxymorphone tablets under single-dose and multiple-dose (steady state) conditions. For the controlled release study, healthy volunteers received a single dose of a 20 mg

controlled release oxymorphone table on the morning of Day 1. Beginning on the morning of Day 3, the volunteers were administered a 20 mg controlled release oxymorphone tablet every 12 hours through the morning dose of Day 9. For the immediate release study, healthy volunteers received a single 10 mg dose of an immediate release oxymorphone tablet on the morning of Day 1. On the morning of Day 3, additional 10 mg immediate release tablets were administered every six hours through the first two doses on Day 9.

FIG. 9 shows the average plasma concentrations of oxymorphone and 6-hydroxyoxymorphone for all subjects after a single dose either controlled release (CR) 20 mg or immediate release (IR) 10 mg oxymorphone. The data in the figure (as with the other relative experimental data herein) is normalized to a 20 mg dose. The immediate release tablet shows a classical curve, with a high, relatively narrow peak followed by an exponential drop in plasma concentration. The controlled release oxymorphone tablets show a lower peak with extended moderate levels of oxymorphone and 6-hydroxy oxymorphone. Table 19 shows the levels of oxymorphone and 6-hydroxy oxymorphone from FIG. 9 in tabular form.

TABLE 19

Mean Plasma Concentration (ng/ml)

	Oxymorphone		6-Hydroxyoxymorphone	
Hour	Controlled Release 20 mg	Immediate Release 10 mg	Controlled Release 20 mg	Immediate Release 10 mg
0.00	0.00	0.00	0.00	0.00
0.25	0.22	1.08	0.14	0.73
0.50	0.59	1.69	0.45	1.22
1.00	0.77	1.19	0.53	0.79
1.50	0.84	0.91	0.53	0.57
2.00	0.87	0.75	0.60	0.47
3.00	0.83	0.52	0.55	0.34
4.00	0.73	0.37	0.53	0.27
5.00	0.94	0.36	0.46	0.23
6.00	0.81	0.28	0.41	0.18
8.00	0.73	0.20	0.37	0.14
10.0	0.60	0.19	0.35	0.15
12.0	0.67	0.25	0.32	0.13
16.0	0.39	0.16	0.29	0.13
24.0	0.23	0.07	0.29	0.13
30.0	0.12	0.01	0.17	0.04
36.0	0.05	0.00	0.11	0.00
48.0	0.00	0.00	0.07	0.01

FIG. 10 shows the average plasma concentrations of oxymorphone and 6-hydroxyoxymorphone for all subjects in the steady state test, for doses of controlled release 20 mg tablets and immediate release 10 mg tablets of oxymorphone. The figure shows the plasma concentrations after the final controlled release tablet is given on Day 9, and the final immediate release tablet is given 12 hours thereafter. The steady state administration of the controlled release tablets clearly shows a steady moderate level of oxymorphone ranging from just over 1 ng/ml to almost 1.75 ng/ml over the course of a twelve hour period, where the immediate release tablet shows wide variations in blood plasma concentration. Table 20 shows the levels of oxymorphone and 6-hydroxyoxymorphone from FIG. 10 in tabular form.

TABLE 20

Summary of Mean Plasma Concentration (ng/ml)

		Oxymorphone		6-Hydroxyoxymorphone	
Day	Hour	Controlled Release 20 mg	Immediate Release 10 mg	Controlled Release 20 mg	Immediate Release 10 mg
4	0.00	1.10	0.75	0.89	0.72
5	0.00	1.12	0.84	1.15	0.88
6	0.00	1.20	0.92	1.15	0.87
7	0.00	1.19	0.91	1.27	1.00
8	0.00	1.19	0.86	1.29	0.98
9	0.00	1.03	1.07	1.09	1.05
	0.25		2.64		1.70
	0.50		3.12	1.50	2.09
	1.00		2.47	1.70	1.68
	1.50		2.05	1.63	1.55
	2.00		1.78	1.64	1.30
	3.00		1.27	1.47	1.11
	4.00		0.98	1.39	0.98
	5.00		1.01	1.21	0.89
	6.00		0.90	1.06	0.84
	6.25		1.17		0.88
	6.50		1.88		1.06
	7.00		2.12		1.20
	7.50		2.24		1.15
	8.00	1.32	2.01	0.97	1.03
	9.00		1.52		0.90
	10.0	1.32	1.24	0.85	0.84
	11.0		1.11		0.74
	12.0	1.18	0.96	0.79	0.70

TABLE 21

Mean Single-Dose Pharmacokinetic Results

	Controlled Release 20 mg		Immediate Release 10 mg	
	oxymorphone	6-OH-oxymorphone	oxymorphone	6-OH-oxymorphone
$AUC_{(0-t)}$	14.74	11.54	7.10	5.66
$AUC_{(0-inf)}$	15.33	16.40	7.73	8.45
C_{max}(ng/ml)	1.12	0.68	1.98	1.40
T_{max}(hr)	5.00	2.00	0.50	0.50
T½(hr)	9.25	26.09	10.29	29.48

Parent 6-OH oxymorphone $AUC_{(0-t)}$ values were lower than the parent compound after administration of either dosage form, but the $AUC_{(0-inf)}$ values are slightly higher due to the longer half-life for the metabolite. This relationship was similar for both the immediate-release (IR) and controlled release (CR) dosage forms. As represented by the average plasma concentration graph, the CR dosage form has a significantly longer time to peak oxymorphone concentration and a lower peak oxymorphone concentration. The 6-OH oxymorphone peak occurred sooner than the parent peak following the CR dosage form, and simultaneously with the parent peak following the IR dosage form.

It is important to note that while the present invention is described and exemplified using 20 mg tablets, the invention may also be used with other strengths of tablets. In each strength, it is important to note how a 20 mg tablet of the same composition (except for the change in strength) would act. The blood plasma levels and pain intensity information are provided for 20 mg tablets, however the present invention is also intended to encompass 5 to 80 mg controlled release tablets. For this reason, the blood plasma level of oxymorphone or 6-hydroxyoxymorphone in nanograms per milliliter of blood, per mg oxymorphone (ng/mg·ml) administered is measured. Thus at 0.02 ng/mg·ml, a 5 mg tablet should produce a minimum blood plasma concentration of 0.1 ng/ml. A stronger tablet will produce a higher blood plasma concentration of active molecule, generally proportionally. Upon administration of a higher dose tablet, for example 80 mg, the blood plasma level of oxymorphone and 6-OH oxymorphone may more than quadruple compared to a 20 mg dose, although conventional treatment of low bioavailability substances would lead away from this conclusion. If this is the case, it may be because the body can only process a limited amount oxymorphone at one time. Once the bolus is processed, the blood level of oxymorphone returns to a proportional level.

It is the knowledge that controlled release oxymorphone tablets are possible to produce and effective to use, which is most important, made possible with the high bioavailability of oxymorphone in a controlled release tablet. This also holds true for continuous periodic administration of controlled release formulations. The intent of a controlled release opioid formulation is the long-term management of pain. Therefore, the performance of a composition when administered periodically (one to three times per day) over several days is important. In such a regime, the patient reaches a "steady state" where continued administration will produce the same results, when measured by duration of pain relief and blood plasma levels of pharmaceutical. Such a test is referred to as a "steady state" test and may require periodic administration over an extended time period ranging from several days to a week or more. Of course, since a patient reaches steady state in such a test, continuing the test for a longer time period should not affect the results. Further, when testing blood plasma levels in such a test, if the time period for testing exceeds the interval between doses, it is important the regimen be stopped after the test is begun so that observations of change in blood level and pain relief may be made without a further dose affecting these parameters.

Study 5-Controlled Release 40 mg vs Immediate Release 4.Times.10 mg under Fed and Fasting Conditions

The objectives of this study were to assess the relative bioavailability of oxymorphone from oxymorphone controlled release (40 mg) compared to oxymorphone immediate release (4.times.10 mg) under both fasted and fed conditions, and to determine the effect of food on the bioavailability of oxymorphone from the controlled release formulation, oxymorphone CR, and from the immediate release formulation, oxymorphone IR.

This study had a single-center, open-label, analytically blinded, randomized, four-way crossover design. Subjects randomized to Treatment 5A and Treatment 5C, as described below, were in a fasted state following a 10-hour overnight fast. Subjects randomized to Treatment 5B and Treatment 5D, as described below, were in the fed state, having had a high fat meal, completed ten minutes prior to dosing. There was a 14-day washout interval between the four dose administrations. The subjects were confined to the clinic during each study period. Subject assigned to receive Treatment 5A and Treatment 5B were discharged from the clinic on Day 3 following the 48-hour procedures, and subjects assigned to receive Treatment 5C and Treatment 5D were discharged from the clinic on Day 2 following the 36-hour procedures. On Day 1 of each study period the subjects received one of four treatments:

Treatments 5A and 5B: Oxymorphone controlled release 40 mg tablets from Table 2. Subjects randomized to Treatment 5A received a single oral dose of one 40 mg oxymorphone controlled release tablet taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 5B received a single oral dose of one 40 mg oxymorphone controlled release tablet taken with 240 ml of water 10 minutes after a standardized high fat meal.

Treatments 5C and 5D: Immediate release tablet (IR) 4.times.10 mg Oxymorphone. Subjects randomized to Treatment 5C received a single oral dose of 4.times.10 mg oxymorphone IR tablet taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 5D received a single oral dose of 4.times.10 mg oxymorphone IR tablet taken with 240 ml of water 10 minutes after a standardized high-fat meal.

A total of 28 male subjects were enrolled in the study, and 25 subjects completed the study. A total of 28 subjects received at least one treatment. Only subjects who completed all 4 treatments were included in the summary statistics and statistical analysis.

Blood samples (7 ml) were collected during each study period at the 0 hour (predose), and at 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 60, and 72 hours post-dose (19 samples) for subjects randomized to all Treatments.

The mean oxymorphone plasma concentration versus time is presented in Table 22. The arithmetic means of the plasma oxymorphone pharmacokinetic parameters and the statistics for all Treatments are summarized in Table 23.

TABLE 22

Mean Plasma Concentration vs. Time (ng/ml)

Time (hr)	Treatment 5A	Treatment 5B	Treatment 5C	Treatment 5D
0	0.00	0.00	0.00	0.00
0.25	0.47	0.22	3.34	1.79
0.50	1.68	0.97	7.28	6.59
0.75	1.92	1.90	6.60	9.49
1	2.09	2.61	6.03	9.91
1.5	2.18	3.48	4.67	8.76
2	2.18	3.65	3.68	7.29
3	2.00	2.86	2.34	4.93
4	1.78	2.45	1.65	3.11
5	1.86	2.37	1.48	2.19
6	1.67	2.02	1.28	1.71
8	1.25	1.46	0.92	1.28
10	1.11	1.17	0.78	1.09
12	1.34	1.21	1.04	1.24

TABLE 22-continued

Mean Plasma Concentration vs. Time (ng/ml)

Time (hr)	Treatment 5A	Treatment 5B	Treatment 5C	Treatment 5D
24	0.55	0.47	0.40	0.44
36	0.21	0.20	0.16	0.18
48	0.06	0.05	0.04	0.05
60	0.03	0.01	0.01	0.01
72	0.00	0.00	0.00	0.00

TABLE 23

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 5

	Treatment 5A		Treatment 5B		Treatment 5C		Treatment 5D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max}	2.79	0.84	4.25	1.21	9.07	4.09	12.09	5.42
T_{max}	2.26	2.52	1.96	1.06	0.69	0.43	1.19	0.62
$AUC_{(0-t)}$	35.70	10.58	38.20	11.04	36.00	12.52	51.35	20.20
$AUC_{(0-inf)}$	40.62	11.38	41.17	10.46	39.04	12.44	54.10	20.26
$T_{1/2el}$	12.17	7.57	10.46	5.45	11.65	6.18	9.58	3.63

The relative bioavailability calculations are summarized in Tables 24 and 25.

TABLE 24

Relative Bioavailability Determination Based on $AUC_{(0-inf)}$

F_{rel} (5D vs. 5C)	F_{rel} (5B vs. 5A)
1.3775	1.0220

TABLE 25

Relative bioavailability Determination Based on $AUC_{(0-24)}$

F_{rel} (5D vs. 5C)	F_{rel} (5B vs. 5A)
1.4681	1.0989

The mean 6-OH oxymorphone plasma concentration versus time is presented in Table 26.

TABLE 26

Mean Plasma Concentration vs. Time (ng/ml)
6-Hydroxyoxymorphone

Time (hr)	Treatment 5A	Treatment 5B	Treatment 5C	Treatment 5D
0	0.00	0.00	0.00	0.00
0.25	0.27	0.05	2.36	0.50
0.50	1.32	0.31	5.35	1.98
0.75	1.37	0.59	4.53	2.97
1	1.44	0.82	3.81	2.87
1.5	1.46	1.09	2.93	2.58
2	1.46	1.28	2.37	2.29
3	1.39	1.14	1.69	1.72
4	1.25	1.14	1.33	1.26
5	1.02	1.00	1.14	1.01
6	0.93	0.86	0.94	0.86
8	0.69	0.72	0.73	0.77
10	0.68	0.67	0.66	0.75
12	0.74	0.66	0.70	0.77
24	0.55	0.52	0.54	0.61
36	0.23	0.30	0.28	0.27

TABLE 26-continued

Mean Plasma Concentration vs. Time (ng/ml)
6-Hydroxyoxymorphone

Time (hr)	Treatment 5A	Treatment 5B	Treatment 5C	Treatment 5D
48	0.18	0.20	0.20	0.19
60	0.09	0.10	0.09	0.09
72	0.06	0.06	0.04	0.05

TABLE 27

Pharmacokinetic Parameters of Plasma
6-Hydroxyoxymorphone for Study 5

	Treatment 5A		Treatment 5B		Treatment 5C		Treatment 5D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max}	1.88	0.69	1.59	0.63	6.41	3.61	3.79	1.49
T_{max}	1.48	1.18	2.73	1.27	0.73	0.47	1.18	0.74
$AUC_{(0-t)}$	28.22	10.81	26.95	11.39	33.75	10.29	32.63	13.32
$AUC_{(0-inf)}$	33.15	11.25	32.98	10.68	37.63	17.01	36.54	13.79
$T_{1/2el}$	17.08	7.45	21.92	8.41	16.01	6.68	16.21	7.42

The above description incorporates preferred embodiments and examples as a means of describing and enabling the invention to be practiced by one of skill in the art. It is imagined that changes can be made without departing from the spirit and scope of the invention described herein and defined in the appended claims.

We claim:

1. An oral controlled release oxymorphone formulation, comprising:

a. about 5 mg to about 80 mg of oxymorphone or a pharmaceutically acceptable salt of oxymorphone; and

b. a hydrophilic material,

wherein upon oral administration of the formulation to a subject in need of an analgesic effect:

(i) the formulation provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone;

(ii) the blood plasma levels of 6-OH oxymorphone and oxymorphone peak within about 1 hour to about 8 hours after administration;

(iii) the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of area under the curve ($AUC_{(0\ to\ inf)}$) of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5;

(iv) the duration of the analgesic effect is through at least about 12 hours after administration; and

(v) the blood plasma levels of oxymorphone exhibit two or three peaks within about 12 hours after administration.

2. The formulation of claim 1 wherein the hydrophilic material is selected from the group consisting of a gum, a cellulose ether, an acrylic resin, a protein-derived material, and mixtures thereof.

3. The formulation of claim 1 wherein the hydrophilic material is a gum selected from the group consisting of a heteropolysaccharide gum, a homopolysaccharide gum, and mixtures thereof.

4. The formulation of claim 3 wherein the gum is selected from the group consisting of xanthan, tragacanth, acacia, karaya, alginates, agar, guar, hydroxypropyl guar, carrageenan, locust bean, and mixtures thereof.

5. The formulation of claim 1 wherein the hydrophilic material is a cellulose ether selected from the group consisting of a hydroxyalkyl cellulose, a carboxyalkyl cellulose, and mixtures thereof.

6. The formulation of claim 1 wherein the hydrophilic material is selected from the group consisting of hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, and mixtures thereof.

7. The formulation of claim 1 wherein the hydrophilic material comprises at least one of:

i. a heteropolysaccharide; or

ii. a heteropolysaccharide and a cross-linking agent capable of cross-linking the heteropolysaccharide; or

iii. a mixture of (i), (ii) and a polysaccharide gum.

8. The formulation of claim 7 wherein the heteropolysaccharide is a water soluble polysaccharide containing two or more kinds of sugar units and having a branched or helical configuration.

9. The formulation of claim 7 wherein the heteropolysaccharide is selected from the group consisting of xanthan gum, deacylated xanthan gum, carboxymethyl ether xanthan gum, propylene glycol ester xanthan gum and mixtures thereof.

10. The formulation of claim 7 wherein the cross-linking agent is a homopolysaccharide gum.

11. The formulation of claim 1 further comprising a hydrophobic polymer.

12. A method of treating pain in a subject in need thereof, the method comprising the step of administering to the subject the formulation of claim 1.

13. A pharmaceutical tablet prepared by:

a. mixing oxymorphone or a pharmaceutically acceptable salt of oxymorphone and controlled release granules comprising a hydrophilic material and one or more optional excipients; and

b. directly compressing the mixture of (a) to form the tablet,

wherein upon placement of the tablet in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.

14. The tablet preparation of claim 13 wherein the hydrophilic material is selected from the group consisting of a gum, a cellulose ether, an acrylic resin, a protein-derived material, and mixtures thereof.

15. The tablet preparation of claim 13 wherein the hydrophilic material is a gum selected from the group consisting of a heteropolysaccharide gum, a homopolysaccharide gum, and mixtures thereof.

16. The tablet preparation of claim 13 wherein the hydrophilic material is a cellulose ether selected from the group consisting of a hydroxyalkyl cellulose, a carboxyalkyl cellulose, and mixtures thereof.

17. The tablet preparation of claim 13 wherein the hydrophilic material is hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, and mixtures thereof.

18. The tablet preparation of claim 13 wherein the hydrophilic material comprises at least one of:

i. a heteropolysaccharide; or

ii. a heteropolysaccharide and a cross-linking agent capable of cross-linking the heteropolysaccharide; or

iii. a mixture of (i), (ii) and a polysaccharide gum.

19. The tablet preparation of claim 18 wherein the heteropolysaccharide is a water soluble polysaccharide containing two or more kinds of sugar units and having a branched or helical configuration.

20. The tablet preparation of claim 19 wherein the heteropolysaccharide is selected from the group consisting of xanthan gum, deacylated xanthan gum, carboxymethyl ether xanthan gum, propylene glycol ester xanthan gum and mixtures thereof.

21. A pharmaceutical tablet prepared by:

a. mixing oxymorphone or a pharmaceutically acceptable salt of oxymorphone and one or more controlled release excipients; and

b. forming the tablet,

wherein upon placement of the tablet in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test; and wherein upon oral administration to a human subject the tablet alleviates pain for 12 to 24 hours.

22. The tablet of claim 21 wherein about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 4 hours in the test, and at least about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test.

23. The tablet of claim 21 wherein at least 27%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test, at least 40%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 2 hours in the test, at least 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 3 hours in the test, at least 64%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 5 hours in the test, at least 70%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 6 hours in the test, at least 79%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 8 hours in the test, at least 85%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test, and at least 89%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 12 hours in the test.

24. The tablet of claim 21, wherein at least 27%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.

25. The tablet of claim 21, wherein at least 40%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 2 hours in the test.

26. The tablet of claim 21, wherein at least 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 3 hours in the test.

27. The tablet of claim 21, wherein at least 64%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 5 hours in the test.

28. The tablet of claim 21, wherein at least 70%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 6 hours in the test.

29. The tablet of claim 21, wherein at least 79%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 8 hours in the test.

30. The tablet of claim 21, wherein at least 85%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test.

31. A method for treating pain in a human subject in need of acute or chronic pain relief, comprising the steps of:

(a) Providing a solid oral dosage form of a controlled release oxymorphone formulation with a release rate profile designed to provide adequate blood plasma levels over at least 12 hours to provide sustained pain relief over this same period comprising about 5 mg to about 80 mg oxymorphone or a pharmaceutically acceptable salt thereof wherein oxymorphone is the sole active ingredient, and wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test; and

(b) administering a single dose of the dosage form to the subject,

wherein the oxymorphone C_{max} is at least 50% higher when the dosage form is administered to the subject under fed as compared to fasted conditions.

32. The method of claim **31** wherein the dosage form comprises about 40 mg oxymorphone or a pharmaceutically acceptable salt thereof, and wherein the oxymorphone C_{max} is about 58% higher when the dosage form is administered to the subject under fed as compared to fasted conditions.

33. The method of claim **31** wherein the dosage form comprises about 20 mg oxymorphone or a pharmaceutically acceptable salt thereof.

34. The method of claim **31** wherein the dosage form comprises about 20 mg to about 40 mg oxymorphone hydrochloride.

35. The method of claim **31** wherein the difference in the oxymorphone area under the curve ($AUC_{(0\text{-}inf)}$ between fed and fasted conditions is less than 20%.

36. The method of claim **35** wherein the difference in $AUC_{(0\text{-}inf)}$ between fed and fasted conditions is about 18%.

37. The method of claim **31** wherein upon oral administration of the dosage form to the subject under fed or fasting conditions:

(i) the dosage form provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone;

(ii) the blood plasma levels of 6-OH oxymorphone and oxymorphone peak within about 1 hour to about 8 hours after administration; and

(iii) the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of $AUC_{(0\text{-}inf)}$ of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5.

38. A method for treating pain in a human subject in need of acute or chronic pain relief, comprising the steps of:

(a) Providing a solid oral dosage form comprising about 5 mg to about 80 mg oxymorphone or a pharmaceutically acceptable salt thereof in a controlled release delivery system with a release rate profile designed to provide adequate blood plasma levels over at least 12 hours to provide sustained pain relief over this same period, wherein oxymorphone is the sole active ingredient, and wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test, about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 4 hours in the test, and at least about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test; and

(b) administering a single dose of the dosage form to the subject,

wherein the oxymorphone C_{max} is at least 50% higher when the dosage form is administered to the subject under fed versus fasted conditions.

39. The method of claim **38** wherein the oxymorphone C_{max} is at least about 58% higher when the dosage form is administered to the subject under fed as compared to fasted conditions.

40. The method of claim **38** wherein the difference in the oxymorphone area under the curve $AUC_{(0\text{-}inf)}$ between fed and fasted conditions is less than 20%.

41. The method of claim **40** wherein the difference in $AUC_{(0\text{-}inf)}$ between fed and fasted conditions is about 18%.

42. The method of claim **38** wherein upon oral administration of the dosage form to the subject under fed or fasting conditions:

(i) the dosage form provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone;

(ii) the blood plasma levels of 6-OH oxymorphone and oxymorphone peak within about 1 hour to about 8 hours after administration; and

(iii) the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of $AUC_{(0\text{-}inf)}$ of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5.

43. The method of claim **38** wherein the system further comprises a hydrophilic material.

44. The method of claim **43** wherein the hydrophilic material is selected from the group consisting of a gum, a cellulose ether, an acrylic resin, a protein-derived material, and mixtures thereof.

45. The method of claim **44** wherein the hydrophilic material is a gum selected from the group consisting of xanthan, tragacanth, acacia, karaya, alginates, agar, guar, hydroxypropyl guar, carrageenan, locust bean, and mixtures thereof.

46. The method of claim **43** wherein the hydrophilic material is a cellulose ether selected from the group consisting of a hydroxyalkyl cellulose, a carboxyalkyl cellulose, and mixtures thereof.

47. The method of claim **43** wherein the hydrophilic material is selected from the group consisting of hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, and mixtures thereof.

48. The method of claim **43** wherein the hydrophilic material comprises at least one of:

a. a heteropolysaccharide; or

b. a heteropolysaccharide and a cross-linking agent capable of cross-linking the heteropolysaccharide; or

c. a mixture of (a), (b) and a polysaccharide gum.

49. An analgesically effective controlled release pharmaceutical composition for oral delivery, comprising:

a. a controlled release delivery system with a release rate profile designed to provide adequate blood plasma levels over at least 12 hours to provide sustained pain relief over this same period; and

b. about 5 mg to about 80 mg of oxymorphone or a pharmaceutically acceptable salt of oxymorphone, wherein oxymorphone is the sole active ingredient,

wherein upon oral administration of a single dose of the composition to a human subject, the oxymorphone C_{max} is at least 50% higher when the dose is administered to the subject under fed as compared to fasted conditions, and wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37°

C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.

50. The composition of claim **49** wherein upon oral administration thereof the oxymorphone $AUC_{(0\text{-}inf)}$ is no more than 20% higher when the dosage form is administered to the subject under fed as compared to fasted conditions.

51. The composition of claim **49** wherein the dosage form comprises about 40 mg oxymorphone, and wherein the oxymorphone C_{max} is about 58% higher when the dosage form is administered to the subject under fed as compared to fasted conditions.

52. The composition of claim **49** wherein the controlled release delivery system comprises a heteropolysaccharide and an agent capable of cross-linking the heteropolysaccharide in presence of gastrointestinal fluid.

53. The composition of claim **52** wherein the heteropolysaccharide and the agent capable of cross-linking the heteropolysaccharide are present in a weight ratio of about 1:3 to about 3:1.

54. The composition of claim **49** wherein about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 4 hours in the test, and at least about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test.

55. An analgesically effective controlled release pharmaceutical composition for oral delivery, comprising:

a. a controlled release delivery system with a release rate profile designed to provide adequate blood plasma levels of oxymorphone and 6-hydroxy-oxymorphone over at least 12 hours to provide sustained pain relief over this same period; and

b. about 5 mg to about 80 mg of oxymorphone or a pharmaceutically acceptable salt of oxymorphone, wherein oxymorphone is the sole active ingredient,

wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.

56. The composition of claim **55**, wherein upon oral administration of a single dose of the composition to a human subject, the oxymorphone C_{max} is at least 50% higher when the dose is administered to the subject under fed as compared to fasted conditions.

57. The composition of claim **55**, wherein the composition is in the form of a tablet and wherein at least 27%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test, at least 40%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 2 hours in the test, at least 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 3 hours in the test, at least 64%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 5 hours in the test, at least 70%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 6 hours in the test, at least 79%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 8 hours in the test, at least 85%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test, and at least 89%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 12 hours in the test.

58. The composition of claim **55**, wherein the composition is in the form of a tablet and wherein at least 27%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.

59. The composition of claim **55**, wherein the composition is in the form of a tablet and wherein at least 40%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 2 hours in the test.

60. The composition of claim **55**, wherein the composition is in the form of a tablet and wherein at least 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 3 hours in the test.

61. The composition of claim **55**, wherein the composition is in the form of a tablet and wherein at least 64%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 5 hours in the test.

62. The composition of claim **55**, wherein the composition is in the form of a tablet and wherein at least 70%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 6 hours in the test.

63. The composition of claim **55**, wherein the composition is in the form of a tablet and wherein at least 79%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 8 hours in the test.

64. The composition of claim **55**, wherein the composition is in the form of a tablet and wherein at least 85%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test.

65. The composition of claim **55**, wherein the composition is in the form of a tablet and wherein at least 89%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 12 hours in the test.

66. An analgesically effective controlled release pharmaceutical composition for oral delivery, comprising:

a. a controlled release delivery system with a release rate profile designed to provide adequate blood plasma levels over at least 12 hours to provide sustained pain relief over this same period; and

b. about 5 mg to about 80 mg of oxymorphone or a pharmaceutically acceptable salt of oxymorphone, wherein oxymorphone is the sole active ingredient,

wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test, and wherein upon oral administration of the composition to a human subject, the blood plasma levels of oxymorphone comprise one or more peaks.

67. The composition of claim **66** wherein the blood plasma levels comprise two peaks.

68. The composition of claim **66** wherein upon oral administration of the composition to a subject in need of an analgesic effect:

(i) the composition provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone;

(ii) the blood plasma levels of 6-OH oxymorphone and oxymorphone peak within about 1 hour to about 8 hours after administration; and

(iii) the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of area under the curve ($AUC_{(0\ to\ inf)}$) of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5.

69. The composition of claim **66** wherein upon oral administration of the composition to a subject in need of an anal-

gesic effect the blood plasma levels of oxymorphone exhibit two or three peaks within about 12 hours after administration.

70. The composition of claim **66** wherein upon oral administration of the composition to a subject in need of an analgesic effect the blood plasma levels of oxymorphone comprise a first peak at about 3 hours after administration and a second peak at about 6-7 hours after administration.

71. The composition of claim **66** wherein the composition is in the form of a tablet and about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 4 hours in the test, and at least about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test.

72. A controlled release pharmaceutical composition comprising oxymorphone or a pharmaceutically acceptable salt thereof as the sole active ingredient and a controlled release matrix, comprising about 10% to about 75% (by total weight of the controlled release matrix) of a gelling agent which forms a gel upon exposure to gastrointestinal fluid;

wherein upon placement of the composition in an in vitro dissolution test comprising USP paddle method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the composition after about 1 hour in the test.

73. The pharmaceutical composition of claim **72** wherein about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the composition after about 4 hours in the test.

74. The pharmaceutical composition of claim **72** wherein at least 80%, by weight, of the oxymorphone or salt thereof is released from the composition after about 10 hours in the test.

75. The pharmaceutical composition of claim **72** wherein upon oral administration of the dosage form to a human subject in need of an analgesic effect, the blood plasma concentration of oxymorphone comprises one or peaks.

76. The pharmaceutical composition of claim **72** wherein upon oral administration of the dosage form to a human subject in need of an analgesic effect, the blood plasma concentration of oxymorphone comprises a first peak at about 3 hours after administration and a second peak at about 6-7 hours after administration; and wherein

(i) the dosage form provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone;

(ii) the blood plasma levels of 6-OH oxymorphone and oxymorphone peak within about 1 hour to about 8 hours after administration;

(iii) the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of area under the curve ($AUC_{(0\ to\ inf)}$) of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5; and

(iv) the duration of the analgesic effect is through at least about 12 hours after administration.

77. A controlled release pharmaceutical composition comprising oxymorphone or pharmaceutically acceptable salt thereof as the sole active ingredient, and a controlled release matrix comprising about 10% to about 75% (by total weight of the controlled release matrix) of a gelling agent which forms a gel upon exposure to gastrointestinal fluid;

wherein upon placement of the composition in an in vitro dissolution test comprising USP paddle method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the composition after about 1 hour in the test, about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the composition after about 4 hours in the test, and at least 80%, by weight, of the oxymorphone or salt thereof is released from the composition after about 10 hours in the test,

wherein upon oral administration of a single dose of the composition to a human subject, the composition provides an oxymorphone C_{max} of at least 50% higher when the dose is administered to the subject under fed as compared to fasted conditions and provides a difference in oxymorphone $AUC_{(0-inf)}$ of less than 20% higher when the dose is administered to the subject under fed as compared to fasted conditions.

78. The pharmaceutical composition of claim **77** wherein upon oral administration of the dosage form to a human subject in need of an analgesic effect the blood plasma level of oxymorphone displays two or three peaks over about the first 12 hours after administration; and

(i) the dosage form provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone;

(ii) the blood plasma levels of 6-OH oxymorphone and oxymorphone peak within about 1 hour to about 8 hours after administration;

(iii) the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of area under the curve ($AUC_{(0\ to\ inf)}$) of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5; and

(iv) the duration of the analgesic effect is through at least about 12 hours after administration.

79. The pharmaceutical composition of claim **77** wherein about 58% to about 66%, by weight, of the oxymorphone or salt thereof is released from the composition after about 4 hours in the test.

80. The pharmaceutical composition of claim **77** wherein about 85% to about 96%, by weight, of the oxymorphone or salt thereof is released from the composition after about 10 hours in the test.

81. A method of treating pain in a subject in need thereof, the method comprising administering to the subject the pharmaceutical composition of claim **72** in an amount sufficient to provide the subject with about 5 mg to about 80 mg of oxymorphone or salt thereof, wherein upon oral administration of a single dose of the composition to a human subject, the composition provides an oxymorphone C_{max} of at least 50% higher when the dose is administered to the subject under fed as compared to fasted conditions and provides a difference in oxymorphone $AUC_{(0-inf)}$ of less than 20% higher when the dose is administered to the subject under fed as compared to fasted conditions.

82. A method of treating pain in a subject in need thereof, the method comprising administering to the subject the pharmaceutical composition of claim **77** in an amount sufficient to provide the subject with about 5 mg to about 80 mg of oxymorphone or salt thereof.

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United States Court of Appeals
for the Federal Circuit

Endo Pharmaceuticals Inc. v Roxane Laboratories, Inc, 2013-1662

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October 2, 2013

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